# Medicaid Dossier for *Avandaryl*

This response may include reference to information about Avandia® (rosiglitazone maleate) Tablets; and Avandaryl® (rosiglitazone maleate and glimepiride) Tablets.

**Some information contained in this response may not be included in the approved Prescribing Information. This response is not intended to offer recommendations for administering this product in a manner inconsistent with its approved labeling.**

**In order for GlaxoSmithKline to monitor the safety of our products, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 888-825-5249. Please consult the attached Prescribing Information.**

**This response was developed according to the principles of evidence-based medicine and, therefore, references may not be all-inclusive.**

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# 1. Change Summary

The purpose of the Change Summary is to provide a description of the significant changes/revisions to the dossier from the previous version(s). The following indicates sections within the dossier that where new clinical data has been added to the dossier within the past year:

- Section 2 Product Summary
- Section 4.10 Warnings/Precautions
- Section 4.11 Adverse Events:
  - The Risk of Myocardial Ischemic Events in Patients Treated with *Avandia*
  - *Avandia* and Fractures
  - Reports of Macular Edema with *Avandia*
- Section 6 Comparative Data:
  - 6.1 Results of the ADOPT Trial
  - 6.2 Risk of Myocardial Ischemic Events with *Avandia* Compared to Actos

## 2. PRODUCT SUMMARY

### About Type 2 Diabetes

- Over 23 million people in the United States have diabetes. Type 2 diabetes accounts for 90-95% of all diagnosed cases. (1)
- Type 2 diabetes is considered one of the most costly diseases in the United States, in part due to its association with microvascular and macrovascular complications.(2)
- Approximately 90% of patients with type 2 diabetes are insulin resistant.(3,4)
- Currently, there are six main classes of oral antidiabetic medications. (5) The thiazolidinedione (TZD) class of agents targets a core underlying defect affecting over 90% of patients with type 2 diabetes, insulin resistance. (3)
- Type 2 diabetes is characterized by a progressive loss of glycemic control marked by an increase in insulin resistance and decline in beta-cell function. (6,7)

### *ABOUT AVANDARYL*

- *Avandaryl* is a fixed-dose combination tablet, which contains two oral antihyperglycemic drugs used in the management of type 2 diabetes providing complimentary mechanisms of action: a TZD (rosiglitazone maleate) and a sulfonylurea (glimepiride).(8)
- *Avandaryl* is indicated as an adjunct to diet and exercise, to improve glycemic control in patients with type 2 diabetes mellitus when treatment with dual *Avandia* (rosiglitazone maleate) and glimiperide therapy is appropriate.(8)
- The combination of *Avandia* 4 or 8 mg/day and a sulfonylurea significantly reduced fasting plasma glucose (FPG) and HbA1c compared to placebo plus sulfonylurea or further up titration of the sulfonylurea in ten 24- to 26- week randomized, double-blind, placebo/active controlled studies and one 2-year double-blind, active-controlled study in older patients (mean age 68 years).(8) *Avandia* 2 mg, 4 mg, or 8 mg daily was administered either once daily (3 studies) or in divided doses twice daily (7 studies), to patients inadequately controlled on a submaximal or maximal dose of sulfonylurea.
- In a 2-year, double-blind study (Study 135) of older patients (age 59-89) on half-maximal sulfonylurea (glipizide 10mg BID) who were randomized to the addition of *Avandia* (4 mg once daily to 8 mg as needed) before titration of glipizide, or to continued up-titration of glipizide, to a maximum of 40 mg/day, 50% of patients treated with *Avandia* 4 or 8 mg/day plus glipizide reached a target HbA1c of < 7% at the last observation in the study compared to those treated with placebo plus up-titrated glipizide. (9) Glycemic control was maintained in patients who received *Avandia* plus glipizide over the 2-year treatment period.
- A 28-week, multicenter, randomized, double-blind, parallel-group study, compared the efficacy and safety of treatment with *Avandaryl* to glimepiride monotherapy and *Avandia* maleate monotherapy in 901 drug-naïve subjects with type 2 diabetes mellitus inadequately controlled on diet and exercise alone. (8,10) Drug naïve subjects were randomized to receive glimepiride monotherapy (1 mg once daily, up-titrated to a maximum of 4 mg once daily), *Avandia* monotherapy (4 mg once daily, up-titrated to a maximum of 8 mg once daily), *Avandaryl* (4 mg/1 mg, up-titrated to a maximum of 4 mg/4 mg once daily), or *Avandaryl* (4 mg/1 mg, up-titrated to a maximum of 8 mg/4 mg once daily) for 28 weeks.
  - Treatment with *Avandaryl* regimens resulted in statistically significant improvements with respect to mean change from baseline in HbA1c and FPG at Week 28 as compared with glimepiride and *Avandia* monotherapies.(8,10) A greater percentage of subjects in the *Avandaryl* groups achieved the HbA1c target of < 7.0% and the HbA1c target of ≤ 6.5.
- In vitro drug metabolism studies suggest that *Avandia* does not inhibit any of the major P450 enzymes at clinically relevant concentrations. Changes in diabetes treatment may be needed based upon clinical response when an inhibitor (such as gemfibrozil) or inducer (such as rifampin) of CYP2C8 is initiated or discontinued during *Avandia* treatment. (8) (11)
- In several pharmacokinetic and/or pharmacodynamic studies, *Avandia* had no clinically significant drug interactions reported with a variety of medications including acarbose, digoxin, ethanol, glimepiride, metformin, nifedipine, oral contraceptives, ranitidine, sucralfate, and warfarin.

[12,13,14,15,16,17,18,19,8] Please refer to the Prescribing Information for *Avandaryl* for additional drug interactions.

***PHARMACOECONOMIC DATA***

- *Avandia* 4 or 8 mg/day and a sulfonylurea (glipizide) were associated with significantly lower total costs compared to a sulfonylurea alone (glipizide).[20]
  - Over a 2-year study period, in addition to improving glycemic control, combination therapy with *Avandia* and a sulfonylurea was associated with significantly fewer hospitalizations (0.37 vs. 0.76 per 1000 patient days, $P = 0.0263$), emergency department (ED) visits (0.59 vs. 1.47 per 1000 patient-days, $P = 0.0006$), and significantly reduced mean length of stay for hospitalizations (4.5 days vs. 7.4 days, $P < 0.001$) compared to sulfonylurea monotherapy.[20] Despite greater medication costs, total direct health care costs were significantly lower for the *Avandia* plus low-dose sulfonylurea group versus the up-titrated sulfonylurea monotherapy group - $480 and $645 per patient per month (PPPM), respectively.

**Important Clinical Considerations When prescribing AVANDIA® (rosiglitazone maleate), AVANDAMET® (rosiglitazone maleate/metformin HCl) and AVANDARYL® (rosiglitazone maleate and glimepiride)**

*Avandia* is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type diabetes.

*Avandamet* is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus when treatment with dual rosiglitazone and metformin therapy is appropriate.

*Avandaryl* is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus when treatment with dual rosiglitazone and glimepiride therapy is appropriate.

**Important Limitations of Use for *Avandia*, *Avandamet*, and *Avandaryl***

- Coadministration of rosiglitazone and insulin is not recommended
- Use of rosiglitazone with nitrates is not recommended

**CONTRAINDICATION FOR *AVANDIa*, *avandamet*, and *avandaryl*:**

- Initiation of rosiglitazone in patients with established New York Heart Association (NYHA) Class III or IV heart failure

**Additional CONTRAINDICATIONS FOR *AVANDAMET*:**

- Renal disease or renal dysfunction. Do not initiate in patients ≥ 80 years of age unless creatinine clearance is normal. Temporarily discontinue *Avandamet* in patients receiving intravascular iodinated contrast materials. Restart *Avandamet* only after normal renal function has been established
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Withhold therapy in the presence of any condition associated with hypoxemia, dehydration, or sepsis

**Additional CONTRAINDICATION FOR *AVANDARYL*:**

- Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin

**Boxed WARNING: For *AVANDIA*, *AVANDAMET* and *AVANDARYL*: CONGESTIVE HEART FAILURE AND MYOCARDIAL ISCHEMIA**

- Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients. Observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of rosiglitazone must be considered
- Rosiglitazone is not recommended in patients with symptomatic heart failure
- A meta-analysis of 42 clinical studies (mean duration 6 months; 14,237 total patients), most of which compared rosiglitazone to placebo, showed rosiglitazone to be associated with an increased

risk of myocardial ischemic events such as angina or myocardial infarction. Three other studies (mean duration 41 months; 14,067 total patients), comparing rosiglitazone to some other approved oral antidiabetic agents or placebo, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive

**For *AVANDAMET*: LACTIC ACIDOSIS**

- **Lactic acidosis is a rare but serious metabolic complication that can occur due to metformin accumulation during therapy with *Avandamet***. The risk of lactic acidosis increases in patients with renal dysfunction, congestive heart failure requiring pharmacologic management, and in the elderly. The onset of lactic acidosis often is subtle and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Patients should be cautioned against excessive alcohol intake when taking *Avandamet*. *Avandamet* should be temporarily discontinued prior to surgical procedures, specifically those involving restricted intake of food and fluids. *Avandamet* should generally be avoided in patients with clinical or laboratory evidence of hepatic disease

**OTHER WARNINGS AND PRECAUTIONS for *AVANDIA*, *AVANDAMET*, and *AVANDARYL***

- Initiation of *Avandia* is not recommended for patients experiencing an acute coronary event and discontinuation of *Avandia* during this event should be considered
- Dose-related edema, weight gain, and anemia may occur
- Rosiglitazone should not be started in patients with active liver disease or with ALT levels >2.5x the upper limit of normal. Check liver enzymes prior to initiation of rosiglitazone and periodically per clinical judgment
- *Avandia*, in combination with other hypoglycemic agents, may increase the risk of hypoglycemia
- Macular edema has been reported
- Increased incidence of bone fracture in female patients
- Resumption of ovulation can occur

***ADDITIONAL CONSIDERATIONS FOR AVANDARYL:***

- Increased risk of cardiovascular mortality was associated with the sulfonylurea tolbutamide. It is prudent to consider that this warning may apply to all sulfonylureas
- Severe hypoglycemia may occur. Elderly, debilitated, or malnourished patients, or patients with adrenal, pituitary, renal, or hepatic insufficiency may be more sensitive to the glucose-lowering effect of sulfonylureas

## 3. DISEASE DESCRIPTION

### *Epidemiology and Risk Factors*

Over 23 million people (7.8% of the population) in the United States have diabetes.[21] Of these, 5.7 million people are not aware that they have the disease. Diabetes was the seventh deadliest disease in the United States in 2006 and is associated with a number of serious microvascular and macrovascular complications.

Type 2 diabetes accounts for 90-95 % of all diagnosed cases of diabetes.[21] The major risk factors for developing type 2 diabetes include a family history of diabetes, overweight or obesity, physical inactivity, race/ethnicity, previously identified impaired glucose tolerance or impaired fasting glucose, hypertension, low high-density lipoprotein (HDL) cholesterol or high triglycerides, a history of gestational diabetes mellitus or delivering a baby weighing > 9 pounds, polycystic ovary syndrome, and a history of cardiovascular disease.[22]

### *Pathophysiology*

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. [23] Type 2 diabetes results from insulin resistance (primarily at the liver, skeletal muscle, and adipose tissue), combined with impaired insulin secretion.[24] Over 90% of patients with type 2 diabetes are insulin resistant. [25] Insulin resistance is often detectable 15 to 20 years before the onset of type 2 diabetes.[26] In addition to being associated with type 2 diabetes, insulin

resistance is also believed to be associated with a cluster of metabolic abnormalities that include impaired glucose tolerance, hypertension, abdominal obesity, dyslipidemia, and prothrombotic and proinflammatory states.[27] Collectively, these components are known as the metabolic syndrome.

When the peripheral tissues do not adequately respond to insulin, there is decreased peripheral glucose uptake.[28] This causes circulating blood glucose concentrations to rise. The resulting hyperglycemia then stimulates the pancreas to augment insulin secretion, leading to hyperinsulinemia. Early in the disease course but before the development of type 2 diabetes, the pancreas is able to overcome insulin resistance and maintain euglycemia. However, as the disease progresses to impaired glucose tolerance and type 2 diabetes, the pancreas is no longer able to provide enough insulin to overcome the body's resistance and hyperglycemia develops.

***Clinical Presentation***

Type 2 diabetes is often asymptomatic in its early stages and therefore can remain undiagnosed for many years.[22] However, patients experiencing symptoms can present with complaints of frequent urination, unusual thirst, extreme hunger, unusual weight loss, extreme fatigue, irritability, frequent infections, blurred vision, cuts/bruises that are slow to heal, tingling/numbness in the hands or feet, and recurring skin, gum, or bladder infections.[29] [23]Many patients remain undiagnosed until they present with one of the complications of diabetes. Long-standing hyperglycemia may result in microvascular complications including retinopathy, nephropathy, and neuropathy or macrovascular complications including cardiovascular disease, cerebrovascular disease, and peripheral vascular disease.

Current American Diabetes Association (ADA) recommendations for the diagnosis of type 2 diabetes are available at www.diabetes.org.

***Approaches to Treatment-Principle Options/Practice Patterns/Place in Therapy***

The management plan for a patient with diabetes should be individualized based on several patient characteristics including age, eating patterns, physical activity, presence of complications, etc. [22] Lifestyle modifications (i.e., diet, exercise, and weight loss) should be the center of any therapeutic program since they have been shown to lower glucose concentrations and may help improve risk factors for microvascular complications and possibly cardiovascular disease. [30]

Pharmacologic treatment of type 2 diabetes includes oral antidiabetic medications that focus mainly on increasing insulin secretion, decreasing hepatic glucose production, or reducing insulin resistance. [30] A summary of the different classes of oral antidiabetic agents is included in Table 1.

Maintaining glycemic control is a key goal in helping to minimize the complications associated with type 2 diabetes. Currently, glycemic treatment goals recommended by the ADA include an A1c of <7%, preprandial plasma glucose of 70-130 mg/dL, and peak postprandial plasma glucose <180 mg/dL.[22] The American Association of Clinical Endocrinologists (AACE) recommends an A1c of ≤ 6.5%, preprandial glucose of ≤ 110 mg/dL, and postprandial glucose ≤ 140 mg/dL.[31] Since diabetes is a progressive disease, the majority of patients will often require more than one medication to treat their diabetes. [32] [33] Data from the United Kingdom Prospective Diabetes Study (UKPDS) found that the proportion of patients able to maintain target glycemic levels with diet, insulin, sulfonylurea, or metformin declined markedly over 9 years of follow-up (~50% of patients achieved target after 3 years of monotherapy; ~25% of patients achieved target after 9 years of monotherapy).[32] Thus, the ability of an agent to maintain glycemic control over the long-term is an important consideration when choosing therapy. If glycemic control cannot be maintained with oral agents alone, insulin may be added as well. [34] There are many obstacles to maintaining glycemic control in type 2 diabetes. Therefore, combination therapy should be promptly initiated.[35]

**Table 1. Therapeutic Options for the Treatment of Type 2 Diabetes[30,35,36,37,38,39,40,41,42,43,44,45,46,47,48]**

| Class | Mechanism of Action | Advantages | Limitations | FDA Indications |
|---|---|---|---|---|
| Sulfonylureas<br>• glyburide, glipizide, glimepiride | ↑ insulin secretion from the pancreas | -Decreases microvascular risk<br>-Convenient daily dosing<br>-Immediate onset of action | -Hypoglycemia<br>-Weight gain<br>-Hyperinsulinemia<br>- Potential increased CV mortality risk | Monotherapy, Combo with insulin, metformin. TZDs, or α-glucosidase inhibitors |
| Biguanides<br>• metformin | Primary ↓ hepatic glucose production | -Weight loss<br>-No hypoglycemia as monotherapy<br>-Decreases macrovascular risk -Potential nonglycemic benefits<br>-Convenient daily dosing | -Adverse GI effects<br>-Contraindicated in patients with renal disease<br>-Contraindicated in patients with CHF requiring pharmacologic treatment<br>-Contraindicated in patients with acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma<br>-Lactic acidosis risk (rare)<br>-Should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials | Monotherapy, Combo with insulin, SU, meglitinides, or TZDs |

*This table is not meant to represent a comprehensive review of these agents. Please refer to the respective Prescribing Information for full details regarding these products; †As measured by homeostasis model assessment (HOMA). Combo = combination therapy; CV = cardiovascular; CHF = congestive heart failure; DPP-4 = dipeptidyl peptidase-4; GI = gastrointestinal; GLP-1 = glucagon-like peptide-1; LFT = liver function test; PPG = post-prandial glucose; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione; SU = sulfonylurea; SCr = serum creatinine; ESRD = end stage renal disease.

| Class | Mechanism of Action | Advantages | Limitations | FDA Indications |
|---|---|---|---|---|
| α-glucosidase inhibitors<br>• acarbose, miglitol | ↓ absorption of carbohydrates in the gut | -Targets PPG<br>-No hypoglycemia as monotherapy<br>-Nonsystemic | -Dosed 3X/day<br>-Adverse GI effects<br>-No long term data<br>-LFT monitoring (acarbose)<br>-Limited information on severely renal impaired patients, SCr > 2.0 mg/dL, therefore, treatment not recommended<br>-Contraindicated in patients with inflammatory bowel disease, colonic ulceration or partial intestinal obstruction and in patients predisposed to intestinal obstruction<br>-Contraindicated in patients with chronic intestinal diseases associated with disorders of digestion or absorption, or conditions that may deteriorate as a result of increased gas formation in the intestine | Monotherapy, Combo with SU |

*This table is not meant to represent a comprehensive review of these agents. Please refer to the respective Prescribing Information for full details regarding these products; †As measured by homeostasis model assessment (HOMA). Combo = combination therapy; CV = cardiovascular; CHF = congestive heart failure; DPP-4 = dipeptidyl peptidase-4; GI = gastrointestinal; GLP-1 = glucagon-like peptide-1; LFT = liver function test; PPG = post-prandial glucose; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione; SU = sulfonylurea; SCr = serum creatinine; ESRD = end stage renal disease.

| Class | Mechanism of Action | Advantages | Limitations | FDA Indications |
|---|---|---|---|---|
| Thiazolidine-diones (TZDs)<br>• rosiglita-zone, pi-oglitazone | Insulin sensitizer, ↑ peripheral glucose disposal | -Minimal risk of hypoglycemia as monotherapy<br>-Targets insulin resistance, a core defect of T2DM<br>- Improves estimates of β-cell function | -Boxed Warning for Congestive Heart Failure<br>-Boxed Warning for Myocardial Ischemia with rosiglitazone<br>-Coadministration of rosiglitazone with insulin is not recommended<br>-Use of rosiglitazone with nitrates is not recommended<br>-Initiation of rosiglitazone is not recommended for patients experiencing an acute coronary event, discontinuation during this acute phase should be considered<br>-Macular edema<br>-Bone fracture<br>-LFT monitoring<br>-Weight gain, edema<br>-Decrease in hemoglobin and hematocrit<br>Rosiglitazone, in combination with other hypoglycemic agents, may increase the risk of hypoglycemia<br>-Increased risk of pregnancy in premenopausal anovulatory women | Monotherapy, Combo therapy with metformin and/or SU |
| Meglitinides/D-phenylalanine derivatives<br>• nateglin-ide, repaglin-ide | ↑ insulin secretion from the pancreas | -Targets PPG<br>- Possible less hypoglycemia and weight gain than with SUs | -Dosed 3X/day<br>-Hypoglycemia<br>-Weight gain<br>- Hyperinsulinemia<br>-No long term data<br>- Upper respiratory tract infection | Monotherapy, Combo with metformin or TZDs |

*This table is not meant to represent a comprehensive review of these agents. Please refer to the respective Prescribing Information for full details regarding these products; †As measured by homeostasis model assessment (HOMA). Combo = combination therapy; CV = cardiovascular; CHF = congestive heart failure; DPP-4 = dipeptidyl peptidase-4; GI = gastrointestinal; GLP-1 = glucagon-like peptide-1; LFT = liver function test; PPG = post-prandial glucose; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione; SU = sulfonylurea; SCr = serum creatinine; ESRD = end stage renal disease.

| Class | Mechanism of Action | Advantages | Limitations | FDA Indications |
|---|---|---|---|---|
| Incretin mimetics/ GLP-1 analogues<br>• exenatide | ↑ insulin secretion from the pancreas, ↓ glucagon secretion from the pancreas | -Sustained glycemic control<br>-Weight loss<br>-Improves estimates of β-cell function | -Subcutaneous injection<br>-Dosed twice daily<br>-Adverse GI side effects<br>- Post-marketing reports of acute pancreatitis<br>Not recommended in patients with ESRD | Combo with metformin, SU, or TZD Combo with metformin and SU, or metformin and TZD |
| Dipeptidyl peptidase-4 (DPP-4) inhibitors<br>• sitagliptin | Slow inactivation of GLP-1 ↑ insulin secretion from the pancreas, ↓ glucagon secretion from the pancreas | -No weight gain<br>-Less hypoglycemia than SU's<br>Good tolerability profile<br>Improves estimates of β-cell function | -Possibility for neurogenic and allergic reactions (theoretical)<br>-Tolerability decreased with decreased DPP-4 specificity<br>- Upper respiratory tract infections, nasopharyngitis, headache<br>- Dosage adjustment with moderate or severe renal insufficiency | Monotherapy, Combo with metformin or TZD |

*This table is not meant to represent a comprehensive review of these agents. Please refer to the respective Prescribing Information for full details regarding these products; †As measured by homeostasis model assessment (HOMA). Combo = combination therapy; CV = cardiovascular; CHF = congestive heart failure; DPP-4 = dipeptidyl peptidase-4; GI = gastrointestinal; GLP-1 = glucagon-like peptide-1; LFT = liver function test; PPG = post-prandial glucose; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione; SU = sulfonylurea; SCr = serum creatinine; ESRD = end stage renal disease.

***Description of Alternate Treatment Options***

The available literature demonstrates that several commonly used natural products can lower blood glucose in patients with diabetes. These products include N-acetylcysteine (NAC), pomegranate, coenzyme Q10, vitamin C, vitamin D, vitamin E, green tea, lutein, zeaxanthin, L-carnitine, cinnamon, magnesium, vanadium sulfate, nopal (prickly pear cactus), fenu-greek, karela (bitter melon), gymnema, ginseng, tronadora, chromium, and alpha-lipoic acid.[49,50]

Gene therapy/transplant (pancreas, islet cell) have more commonly been utilized in type 1 diabetes, but preliminary studies have evaluated its use in type 2 diabetes.[51]

## 4. PRODUCT DESCRIPTION

### 4.1 Generic Name, Brand Name and Therapeutic Class

**Generic Name:** Rosiglitazone maleate and glimepiride

**Brand Name:** Avandaryl®

**Therapeutic Class:** Fixed-dose thiazolidinedione/sulfonylurea tablet

### 4.2 Dosage Forms, Package Sizes, and NDC

***Dosage Forms/National Drug Code***

- - 4 mg/1 mg (yellow, rounded triangular tablet, gsk debossed on one side and 4/1 on the other)
  - bottles of 30: 0007-3151-13
- - 4 mg/2 mg (orange, rounded triangular tablet, gsk debossed on one side and 4/2 on the other)

  - bottles of 30: 0007-3152-13
- - 4 mg/4 mg (pink, rounded triangular tablet, gsk debossed on one side 4/4 on the other)
  - bottles of 30: 0007-3153-13
- - 8 mg/2 mg (pale pink, rounded triangular tablet, gsk debossed on one side 8/2 on the other)
  - bottles of 30: 0007-3148-13
- - 8 mg/4 mg (red, rounded triangular tablet, gsk debossed on one side 8/4 on the other)
  - bottles of 30: 0007-3149-13

**4.3 AWP and WAC Cost Per Unit**

Wholesale Acquisition Cost (WAC)/tab

- 4 mg/1 mg: $3.50
- 4 mg/2 mg: $3.50
- 4 mg/4 mg: $3.50
- 8 mg/2 mg: $6.02
- 8 mg/4 mg: $6.02

**4.4 AHFS or Other Drug Classification**

**DPS/AHFS Drug Classification:** 36.26 Diabetes Mellitus

**4.5 FDA Approved Indications**

Refer to Enclosed Prescribing Information.

**Date of FDA Approval:** November 23, 2005

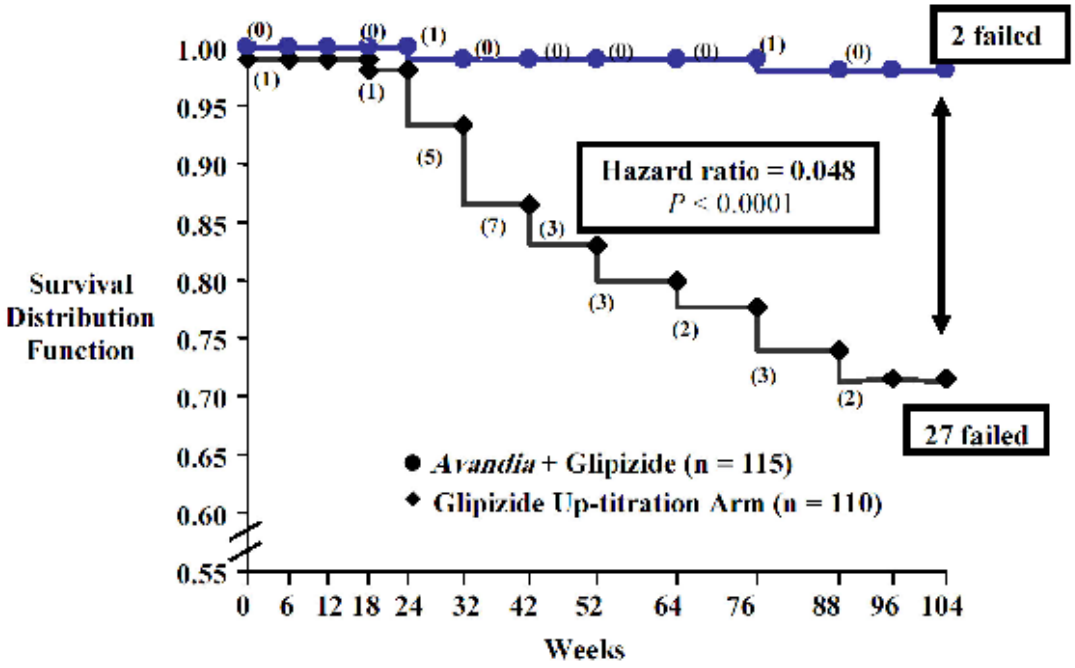
**4.6 Use in Special Populations**

***Efficacy and Safety of Avandia in Combination with a Sulfonylurea in Elderly Patients with Type 2 Diabetes***

A 2-year, randomized, double-blind study (Study 135) was conducted to compare the efficacy and safety of *Avandia* (N = 116) versus placebo (N = 111) in combination with glipizide in elderly patients with type 2 diabetes inadequately controlled on glipizide monotherapy. [9] The majority of patients were male (73%) with a mean age of 68 years, and mean disease duration of 6.8 years. A run-in period of 4 weeks (patients received glipizide 10 mg twice daily and *Avandia*-matched placebo once daily) was followed by a 2-year treatment period with double-blind study medication (patients were randomized to *Avandia* 4 mg once daily plus glipizide 10 mg twice daily or placebo plus glipizide 10 mg twice daily). During the treatment period, up-titration occurred at the discretion of the investigator with the goal being to reach the American Diabetes Association (ADA) glycemic target (HbA1c < 7%). Titration was required if the patient's fasting plasma glucose (FPG) was ≥10 mmol/L. The first up-titration was with *Avandia* to 4 mg twice daily or matched placebo. Further up-titrations were with glipizide from 20 mg/day to 30 mg/day and then to 40 mg/day. The primary endpoint of the study was the time from randomization to the final action point (FAP), which was defined as the time to reach FPG ≥10 mmol/L (confirmed by repeat measurement) while at maximum doses of *Avandia* and glipizide.

Loss of glycemic control (FPG ≥ 10 mmol/L, achievement of FAP) occurred in a significantly lower proportion of patients (2%) on *Avandia* plus glipizide compared to patients in the glipizide up-titration arm (28.7%). [9] The survival distribution curve for the time to FAP is shown in Figure 1.

**Figure 1. RESULT: Time to Reach Final Action Point [9]**

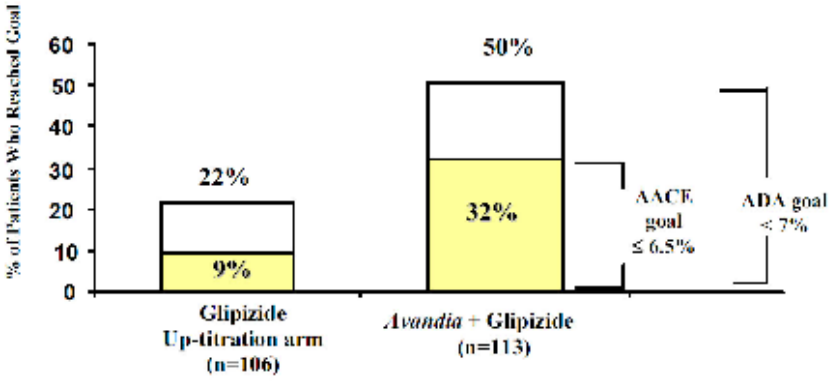



About 78% of the patients on combination therapy completed the 2 years of therapy while 51% completed therapy in the glipizide up-titration arm. Thirteen patients treated with *Avandia* required titration to maximum dose glipizide compared to 53 patients in the glipizide up-titration arm. The hazard ratio suggesting that *Avandia* plus glipizide treatment reduced the risk of requiring maximum glipizide to control hyperglycemia by an estimated 84% relative to placebo plus glipizide treatment was 0.155 ([95% Confidence Interval (CI) 0.083, 0.287], $P < 0.0001$).[52] Fifty-nine patients of 115 patients (51%) in the *Avandia* arm were able to complete the study and maintain glycemic control with *Avandia* 4 mg once daily plus sub-maximal glipizide (glipizide 10 mg twice daily). [9]

Mean baseline FPG and HbA1c were 8.71 mmol/L and 7.72%, respectively, for the *Avandia* plus glipizide arm and 8.84 mmol/L and 7.65%, respectively, for the glipizide up-titration arm. The effect of combination therapy on FPG and HbA1c was durable over the 2 year study period, with patients achieving a mean of 7.39 mmol/L for FPG and a mean of 6.98% for HbA1c compared to no change on the glipizide up-titration arm.

The percent of patients achieving the ADA and American Association of Clinical Endocrinologists (AACE) glycemic targets at the last observation in the study are presented in Figure 2.

**Figure 2. Patients Achieving ADA and AACE HbA1c Target [9,52]**




The effect of *Avandia* plus glipizide versus up-titrated glipizide on insulin resistance and beta-cell function was also evaluated in this study. Results were measured using homeostasis model assessment (HOMA); a mathematical model that estimates insulin resistance and beta-cell function from fasting insulin and glucose values. This was a repeated measures analysis accounting for the baseline value, treatment, visit and treatment-visit interactions and the correlation among the visits within a patient. *Avandia* plus glipizide decreased estimates of insulin resistance by 14% from baseline ($P = 0.001$) compared to an increase of 18% with up-titrated glipizide alone ($P = 0.0028$). The difference between treatment groups was statistically significant ($P < 0.0001$). [9] *Avandia* plus glipizide increased estimates of beta-cell function by 56% from baseline ($P < 0.0001$) compared to a 6% increase with up-titrated glipizide alone ($P = 0.4059$). The difference between treatment groups was statistically significant ($P < 0.0001$).[52]

Patients were more frequently withdrawn from the study due to deterioration of glycemic control in the uptitrated glipizide group. This different rate of withdrawal resulted in a different mean duration of drug exposure in the two groups (644 days with *Avandia* plus glipizide; 560 days with uptitrated glipizide alone). [9]Despite this difference in drug exposure, the number of patients reporting at least one adverse event was similar in the *Avandia* plus glipizide (N = 116) and the glipizide up-titration (N = 111) arms (95.7% vs. 93.7%, respectively).[52] The most frequently occurring on-therapy adverse events in the *Avandia* plus glipizide and glipizide uptitration alone groups were upper respiratory tract infection (34.5% vs. 44.1%), symptomatic hypoglycemia (31.9% vs. 27.0%), and injury (31% vs. 20.7%).

Of note, there were no discontinuations due to hypoglycemia reported with *Avandia* plus glipizide or up-titrated glipizide alone.[52] The incidence of adverse events related to edema was 23% and 9% in the *Avandia* plus glipizide and glipizide uptitration alone groups, respectively. All cases of edema were characterized by the investigator as mild to moderate in nature and infrequently led to discontinuation from therapy (2 patients). Congestive heart failure was reported at a rate of 3.4% and 2.7% in the *Avandia* plus glipizide and glipizide uptitration alone groups, respectively. [9,52] Mean body weight increased by 4.3 kg with *Avandia* plus glipizide (n = 89) and decreased by 1.2 kg (n = 54) with up-titrated glipizide over the 2-year study period. [9,52]

**4.7 Pharmacology**

Refer to Enclosed Prescribing Information.

**4.8 Pharmacokinetics/Pharmacodynamics**

Refer to Enclosed Prescribing Information.

**4.9 Contraindications**

Refer to Enclosed Prescribing Information.

**4.10 Warnings/Precautions**

**WARNING: CONGESTIVE HEART FAILURE AND MYOCARDIAL ISCHEMIA**

- **Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients. After initiation of *Avandaryl*, and after dose increases, observe patients carefully for sign and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of *Avandaryl* must be considered.**
- ***Avandaryl* is not recommended in patients with symptomatic heart failure. Initiation of *Avandaryl* in patients with established NYHA Class III or IV heart failure is contraindicated.**
- **A meta-analysis of 42 clinical studies (mean duration 6 months; 14,237 total patients), most of which compared rosiglitazone to placebo, showed rosiglitazone to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction. Three other studies (mean duration 41 months; 14,067 total patients), comparing rosiglitazone to some other approved oral antidiabetic agents or placebo, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive.**

Refer to Enclosed Prescribing Information.

**4.11 Adverse Events**

***General***

Refer to Enclosed Prescribing Information.

***The Risk of Myocardial Ischemic Events in Patients treated with Avandia***

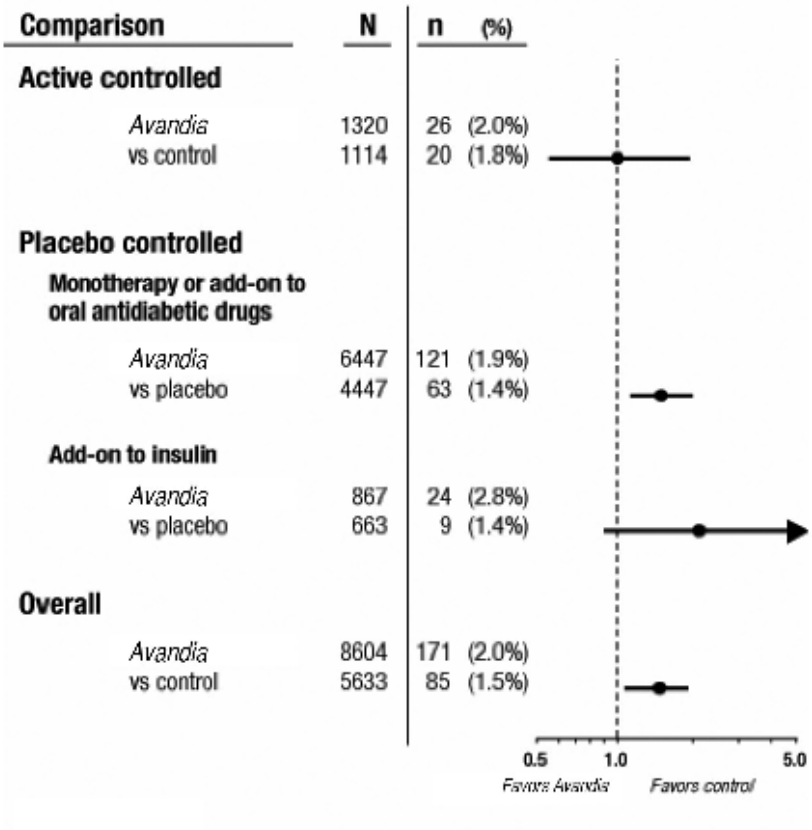
**FDA Meta-Analysis of Myocardial Ischemia in a Group of 42 Clinical Trials[42]**

A meta-analysis was conducted retrospectively to assess cardiovascular adverse events reported across 42 double-blind, randomized, controlled clinical trials (mean duration 6 months).[53] These studies had been conducted to assess glucose-lowering efficacy in type 2 diabetes, and prospectively planned adjudication of cardiovascular events had not occurred in the trials. Some trials were placebo-controlled and some used active oral antidiabetic drugs as controls. Placebo-controlled studies included monotherapy trials (*Avandia* monotherapy versus placebo monotherapy) and add-on trials (*Avandia* or placebo, added to sulfonylurea, metformin, or insulin). Active control studies included monotherapy trials (*Avandia* monotherapy versus sulfonylurea or metformin monotherapy) and add-on trials (*Avandia* plus sulfonylurea or *Avandia* plus metformin, versus sulfonylurea plus metformin). A total of 14,237 patients were included (8,604 in treatment groups containing *Avandia*, 5,633 in comparator groups), with 4,143 patient-years of exposure to *Avandia* and 2,675 patient-years of exposure to comparator. Myocardial ischemic events included angina pectoris, angina pectoris aggravated, unstable angina, cardiac arrest, chest pain, coronary artery occlusion, dyspnea, myocardial infarction, coronary thrombosis, myocardial ischemia, coronary artery disease, and coronary artery disorder. In this analysis, an increased risk of myocardial ischemia with *Avandia* versus pooled comparators was observed (2% *Avandia* versus 1.5% comparators, odds ratio [OR] 1.4, 95% confidence interval [CI] 1.1, 1.8). An increased risk of myocardial ischemic events with *Avandia* was observed in the placebo-controlled studies, but not in the active-controlled studies. (See Figure 3) A greater increased risk of myocardial ischemic events was observed in studies where *Avandia* was added to insulin (2.8% for *Avandia* plus insulin versus 1.4% for placebo plus insulin, [OR 2.1, 95% CI 0.9, 5.1]). This increased risk reflects a difference of 3 events per 100 patient years (95% CI -0.1, 6.3) between treatment groups.

In studies in which *Avandia* was added to insulin, *Avandia* increased the risk of congestive heart failure and myocardial ischemia.[42] Coadministration of *Avandia* and insulin is not recommended. In five, 26-week, controlled, randomized, double-blind trials which were included in the meta-analysis, patients with type 2 diabetes mellitus were randomized to coadministration of *Avandia* and insulin (N = 867) or insulin (N = 663). In these 5 trials, *Avandia* was added to insulin. These trials included patients with long-standing diabetes (median duration of 12 years) and a high prevalence of pre-existing medical conditions, including peripheral neuropathy, retinopathy, ischemic heart disease, vascular disease, and

congestive heart failure. The total number of patients with emergent congestive heart failure was 21 (2.4%) and 7 (1.1%) in the *Avandia* plus insulin and insulin groups, respectively. The total number of patients with emergent myocardial ischemia was 24 (2.8%) and 9 (1.4%) in the *Avandia* plus insulin and insulin groups, respectively (OR 2.1 [95% CI 0.9, 5.1]). Although the event rate for congestive heart failure and myocardial ischemia was low in the studied population, consistently the event rate was 2-fold or higher with coadministration of *Avandia* and insulin. These cardiovascular events were noted at both the 4 mg and 8 mg daily doses of *Avandia*.

**Figure 3. Forest Plot of Odds Ratios (95% Confidence Intervals) for Myocardial Ischemic Events in the Meta-Analysis of 42 Clinical Trials**



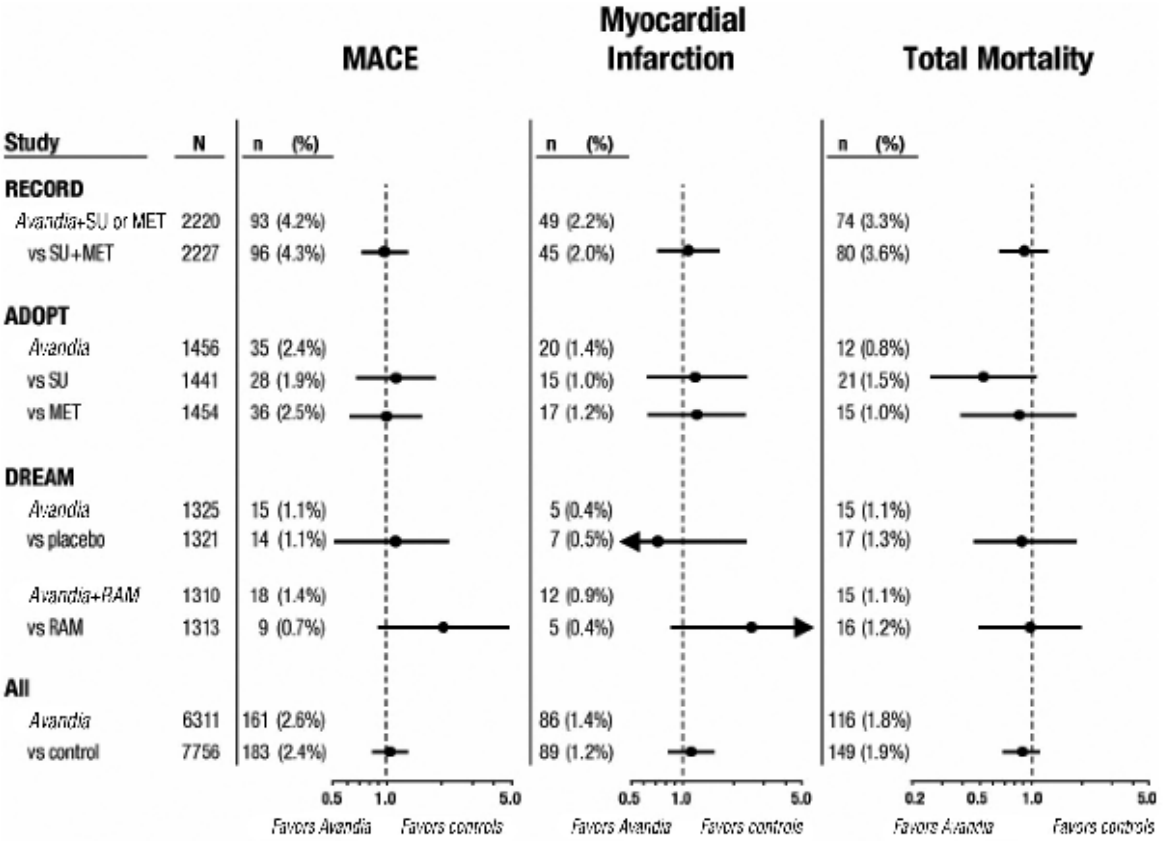

A greater increased risk of myocardial ischemia was also observed in patients who received *Avandia* and background nitrate therapy. For *Avandia* (N = 361) versus control (N = 244) in nitrate users, the odds ratio was 2.9 (95% CI 1.4, 5.9), while for non-nitrate users (about 14,000 patients total), the odds ratio was 1.3 (95% CI 0.9, 1.7). This increased risk represents a difference of 12 myocardial ischemic events per 100 patient years (95% CI 3.3, 21.4). Most of the nitrate users had established coronary heart disease. Among patients with known coronary heart disease who were not on nitrate therapy, an increased risk of myocardial ischemic events for *Avandia* versus comparator was not demonstrated. Use of *Avandia* with nitrates is not recommended.

**Myocardial Ischemic Events in Large Long-Term Prospective Randomized Controlled Trials of *Avandia*[42]**

Data from 3 other large long-term prospective randomized controlled clinical trials of *Avandia* were assessed separately from the meta-analysis. These 3 trials include a total of 14,067 patients (treatment groups containing *Avandia* N = 6,311, comparator groups N = 7,756), with patient-year exposure of 21,803 patient-years for *Avandia* and 25,998 patient-years for comparator. Duration of follow-up exceeded 3 years in each study. ADOPT (A Diabetes Outcomes Progression Trial) was a 4- to 6-year randomized, active-controlled study in recently diagnosed patients with type 2 diabetes naïve to drug therapy.[54] It was an efficacy and general safety trial that was designed to examine the durability of *Avandia* as monotherapy (N = 1,456) for glycemic control in type 2 diabetes, with comparator arms of sulfonylurea monotherapy

(N = 1,441) and metformin monotherapy (N = 1,454). DREAM (Diabetes Reduction Assessment with Rosiglitazone and Ramipril Medication) was a 3- to 5-year randomized, placebo-controlled study in patients with impaired glucose tolerance and/or impaired fasting glucose.(55) It had a 2x2 factorial design, intended to evaluate the effect of *Avandia*, and separately of ramipril (an angiotensin converting enzyme inhibitor [ACEI]), on progression to overt diabetes. In DREAM, 2,635 patients were in treatment groups containing *Avandia*, and 2,634 were in treatment groups not containing *Avandia*. Interim results have been published for RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes), an ongoing open-label, 6-year cardiovascular outcomes study in patients with type 2 diabetes with an average treatment duration of 3.75 years.(56) RECORD includes patients who have failed metformin or sulfonylurea monotherapy; those who have failed metformin are randomized to receive either add-on *Avandia* or add-on sulfonylurea, and those who have failed sulfonylurea are randomized to receive either add-on *Avandia* or add-on metformin. In RECORD, a total of 2,220 patients are receiving add-on *Avandia*, and 2,227 patients are on one of the add-on regimens not containing *Avandia*. For these 3 trials, analyses were performed using a composite of major adverse cardiovascular events (cardiovascular death, myocardial infarction, and stroke), referred to hereafter as MACE. This endpoint differed from the meta-analysis's broad endpoint of myocardial ischemic events, more than half of which were angina. Myocardial infarction included adjudicated fatal and nonfatal myocardial infarction plus sudden death. As shown in Figure 4, the results for the three endpoints (MACE, MI, and Total Mortality) were not statistically significantly different between *Avandia* and comparators.

**Figure 4. Hazard Ratios for the Risk of MACE (Myocardial Infarction, Cardiovascular Death, or Stroke), Myocardial Infarction, and Total Mortality With Avandia Compared With a Control Group**




SU = sulfonylurea; MET = metformin; RAM = ramipril

In preliminary analyses of the DREAM trial, the incidence of cardiovascular events was higher among subjects who received *Avandia* in combination with ramipril than among subjects who received ramipril alone, as illustrated in Figure 2. This finding was not confirmed in ADOPT and RECORD

(active-controlled trials in patients with diabetes) in which 30% and 40% of patients respectively, reported ACE-inhibitor use at baseline.

In their entirety, the available data on the risk of myocardial ischemia are inconclusive. Definitive conclusions regarding this risk await completion of an adequately-designed cardiovascular outcome study. There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with *Avandia* or any other oral antidiabetic drug.

***Reported Incidence of Hypoglycemia with Avandaryl***

**Clinical Information**

In the 28-week double-blind trial of *Avandaryl* in drug-naïve patients with type 2 diabetes, confirmed hypoglycemia was reported in 3.6%, 5.5%, 4.1%, and 0.4% of patients in the *Avandaryl* 4 mg/4 mg, *Avandaryl* 8 mg/4 mg, glimepiride and rosiglitazone treatment groups, respectively.[10] Patients in this trial were started on *Avandaryl* 4 mg/1 mg, rosiglitazone 4 mg, or glimepiride 1 mg. Doses could be increased at 4-week intervals to reach a maximum total daily dose of either 4 mg/4 mg or 8 mg/4 mg for *Avandaryl*, 8 mg for rosiglitazone monotherapy or 4 mg for glimepiride monotherapy. Hypoglycemia was reported to be generally mild to moderate in intensity and none of the reported events of hypoglycemia resulted in withdrawal from the study.[8] Hypoglycemia requiring parenteral treatment (i.e., intravenous glucose or glucagon injection) was observed in 3 (0.7%) patients treated with *Avandaryl*.

Nine 24 to 26-week double-blind, randomized clinical studies (Studies 127, 132, 143, 145, 147, 162, 015, 079, 096) were conducted to evaluate the effectiveness and safety of *Avandia* in combination with a sulfonylurea compared to placebo plus a sulfonylurea.[57,58,59,60,61,62,63,64,65] Pooled adverse events of hypoglycemia reported during these pre-approval studies are presented in Table 2. Reporting of hypoglycemic events in the clinical trials with *Avandia* and a sulfonylurea was based on patient symptoms and was not systematically verified by glucose testing. Symptoms of hypoglycemia appeared to be dose-related and were typically mild to moderate in severity.

**Table 2. Hypoglycemia with *Avandia* in Combination with a Sulfonylurea**

| | N | Adverse Experience of Hypoglycemia (%) |
|---|---|---|
| ***Avandia* 4 mg/day + Sulfonylurea** | 622 | 6.8 |
| ***Avandia* 8 mg/day + Sulfonylurea** | 885 | 11.8 |
| **Sulfonylurea** | 1213 | 3.3 |

In a 2-year randomized, double-blind, active-controlled study (Study 135), elderly patients (mean age 68.4 years) inadequately controlled on half-maximal sulfonylurea therapy (glipizide 10 mg twice daily) were randomized to the addition of *Avandia* (n = 115, 4 mg once daily to 8 mg as needed) before titration of glipizide, or to continued up-titration of glipizide (n = 110), to a maximum of 20 mg twice daily. [9] Symptomatic hypoglycemia data were collected through patient reports of suspected symptoms and did not require confirmation or documentation of glucose levels. The incidence of symptomatic hypoglycemia was similar between treatment groups: 32% for the *Avandia* plus glipizide group and 27% for the up-titrated glipizide group.

A 24-week, randomized, double-blind study has evaluated the efficacy and safety of rosiglitazone in combination with submaximal therapeutic doses of glimepiride in patients with type 2 diabetes inadequately controlled on non-thiazolidinedione oral antidiabetic monotherapy.[66,67] During a 6-week run-in period, patients discontinued their current antidiabetic medication and received glimepiride 2 mg/day plus placebo. All patients were randomized to receive rosiglitazone 4 mg/day plus glimepiride 2 mg/day (titratable to 4 mg/day after 8 weeks) or glimepiride 4 mg/day (titratable to 8 mg/day after 8 weeks) plus placebo for 24 weeks.

The incidence of hypoglycemia was 20.9% with rosiglitazone 4 mg plus glimepiride (41/196) compared to 13.3% (26/195) with glimepiride plus placebo. One patient in the glimepiride plus placebo group withdrew from the study due to severe hypoglycemia.

***Weight Gain with Avandaryl***

**Pre-approval Data**

Nine 24 to 26-week double-blind, randomized clinical studies (Studies 015, 079, 096, 127, 132, 143, 145, 147 and 162) were conducted to evaluate the effectiveness and safety of *Avandia* in combination with a sulfonylurea compared to placebo plus a sulfonylurea.[57,58,59,60,61,62,63,65,68] Median weight changes from the pooled data of these pre-approval studies are presented in Table 3.

**Table 3. Weight Changes (kg) from Baseline During Clinical Trials with *Avandia* in Combination with a Sulfonylurea**

| **Regimen** | | **Control Group** | | ***Avandia*** **4 mg/day** | ***Avandia*** **8 mg/day** |
|---|---|---|---|---|---|
| Combination Therapy | Duration | | Median (25th, 75th percentile) | Median (25th, 75th percentile) | Median (25th, 75th Percentile) |
| Sulfonylurea | 24-26 weeks | Sulfonylurea | 0 (-1.0, 1.3) n = 1155 | 2.2 (0.5, 4.0) n = 613 | 3.5 (1.4, 5.9) n = 841 |

**Additional Studies**

An additional 26-week, double-blind, placebo-controlled study (Study 234) evaluated the combination of *Avandia* plus glimepiride in 172 patients with type 2 diabetes.[69] Following a variable open-label titration period to a daily dosage of glimepiride 3 mg (dosage strength not commercially available in the US) and then a single-blind run-in period with glimepiride 3 mg once daily and placebo, patients were randomized to receive the add-on of *Avandia* 4 mg once daily, *Avandia* 8 mg once daily, or placebo. A mean trend towards an increase in body weight was observed among patients receiving *Avandia*, which was more pronounced in the *Avandia* 8 mg group (mean increase of 1.7 ± 3.6 kg compared to 0.9 ± 3.7 in the *Avandia* 4 mg group). Mean body weight remained stable in the placebo group.

A 24-week, randomized, double-blind study (Study 325) has evaluated the efficacy and safety of *Avandia* in combination with glimepiride in patients with type 2 diabetes inadequately controlled on non-thiazolidinedione oral antidiabetic monotherapy. [66] During a 6-week run-in period, patients discontinued their current antidiabetic medication and received glimepiride 2 mg/day plus placebo. Patients inadequately controlled on glimepiride 2 mg/day were randomized to receive *Avandia* 4 mg/day plus glimepiride 2 mg/day (titratable to 4 mg/day after 8 weeks) or glimepiride 4 mg/day (titratable to 8 mg/day after 8 weeks) plus placebo for 24 weeks. Mean increases in body weight of 3.8 ± 3.64 kg and 1.80 ± 4.41 kg were noted in the *Avandia* plus glimepiride and glimepiride groups, respectively. All cases of weight gain were considered to be of mild or moderate severity.

A 2-year, randomized, double-blind study (Study 135) was conducted to compare the efficacy and safety of *Avandia* (N = 116) versus placebo (N = 111) in combination with glipizide in elderly patients (mean age 68 years) with type 2 diabetes inadequately controlled on glipizide therapy. [9] A run-in period of 4 weeks (patients received glipizide 10 mg twice daily and *Avandia*-matched placebo once daily) was followed by a two-year treatment period with double-blind study medication (patients were randomized to *Avandia* 4 mg once daily plus glipizide 10 mg twice daily or placebo plus glipizide 10 mg twice daily). During the treatment period, uptitration occurred at the discretion of the investigator with the goal being to reach the American Diabetes Association glycemic target (HbA1c < 7 %). Titration was required if the patient's fasting plasma glucose (FPG) was ≥10 mmol/L. The first uptitration was with *Avandia* to 4 mg twice daily or matched placebo. Further uptitrations were of glipizide from 20 mg/day to 30 mg/day and then to 40 mg/day. The mean weight change overtime for patients with a value at week 104 was +4.3 kg and -1.2 kg with *Avandia* a 4 or 8 mg/day plus glipizide (n = 89) and up-titrated glipizide (n = 54), respectively.

A 28-week, multicenter, randomized, double-blind study (Study 004), compared the efficacy and safety of *Avandaryl* 4mg/4mg and 8mg/4mg as compared with glimepiride and rosiglitazone monotherapy in 901 drug-naive subjects with type 2 diabetes.[10] The median increase in weight from baseline (25th, 75th percentile) to week 28 was 2.00 kg (0.00, 4.60) and 3.40 kg (0.45, 6.30) for the *Avandaryl* 4mg/4mg and 8mg/4mg groups respectively, as compared with an increase of 1.10 kg (-1.20, 3.30) and 1.00 kg (-1.00, 3.55) with glimepiride and rosiglitazone monotherapy respectively.

**Post-marketing Surveillance Data**

In postmarketing experience, there have been reports of unusually rapid increases in weight and increases in excess of that generally observed in clinical trials.(42) Patients who experience such increases should be assessed for fluid accumulation and volume-related events such as excessive edema and congestive heart failure.

***Reports of Fluid Related Events with Avandia***

**Clinical Information**

**Edema**

*Avandia* should be used with caution in patients with edema.(42) In controlled clinical trials of patients with type 2 diabetes, mild to moderate edema was reported in patients treated with *Avandia* (Table 4). The event usually did not require discontinuation of treatment with *Avandia* and tended to be reported more frequently at higher doses. Patients with ongoing edema are more likely to have adverse events associated with edema if started on combination therapy with insulin and *Avandia*. Coadministration of *Avandia* and insulin is not recommended.

**Table 4. Incidence of Edema with *Avandia* in Controlled Clinical Trials of Type 2 Diabetes Patients**

| Treatment Group | N | % |
|---|---|---|
| *Avandia* monotherapy(42)* | 2526 | 4.8 |
| *Avandia* 4 or 8 mg/day + metformin(70)† | 338 | 4.4 |
| *Avandia* 8 mg/day + sulfonylurea(42) | 885 | 12.4 |
| *Avandia* 4 or 8 mg/day + metformin + sulfonylurea(71) | 561 | 12.1 |
| *Avandia* + insulin(42)‡ | 408 | 14.7 |
| Placebo(42) | 601 | 1.3 |
| Metformin(42) | 225 | 2.2 |
| Sulfonylurea(42) | 626 | 1.0 |
| Metformin + sulfonylurea(71) | 276 | 4.0 |
| Insulin(42) | 203 | 5.4 |
| *Includes all doses studied, majority of patients received *Avandia* 4 or 8 mg/day. †*Avandia* added to maximum doses of metformin. ‡Includes patients on *Avandia* 4 or 8 mg/day. Coadministration of *Avandia* and insulin is not recommended. | | |

**Congestive Heart Failure (CHF)**

*Avandia*, like other thiazolidinediones, alone or in combination with other antidiabetic agents, can cause fluid retention, which may exacerbate or lead to heart failure.(42) Patients should be observed for signs and symptoms of heart failure. If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of *Avandia* must be considered. *Avandia* is not recommended in patients with symptomatic heart failure. Initiation of *Avandia* in patients with established NYHA Class III and IV heart failure is contraindicated.

In five, 26-week, controlled, randomized, double-blind trials, patients with type 2 diabetes were randomized to coadministration of *Avandia* and insulin (N = 867) or insulin (N = 663).(42) In these 5 trials, *Avandia* was added to insulin. These trials included patients with long-standing diabetes (median duration of 12 years) and a high prevalence of pre-existing medical conditions, including peripheral neuropathy, retinopathy, ischemic heart failure, vascular disease, and congestive heart failure. The total number of patients with emergent CHF was 21 (2.4%) and 7 (1.1%) in the *Avandia* plus insulin and insulin groups, respectively. These cardiovascular events were noted at both the 4 mg and 8 mg daily doses of *Avandia*. Coadministration of *Avandia* and insulin is not recommended.

Reports of CHF from an integrated clinical trials analysis (ICT), DREAM, ADOPT, and RECORD interim analysis remain consistent with previous reports and observations from individual and pooled controlled clinical trials of an increased incidence of CHF in patients treated with *Avandia*.(54,55,56,72)

***Avandia* vs. Placebo in Type 2 Diabetes Patients with NYHA Class I or II CHF**

A 52-week, double-blind, placebo-controlled, non-inferiority echocardiographic study was conducted in 224 patients with type 2 diabetes and NYHA Class I or II CHF.(73) Patients with an ejection fraction ≤ 45% treated with angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs)

and/or diuretics at study entry were randomized to *Avandia* (4 mg/day increased to 8 mg/day) or placebo in addition to background antidiabetic therapy. Background antidiabetic therapy included diet, exercise and/or oral monotherapy or oral combination therapy of no more than 2 medications (insulin therapy was excluded at entry to the study and was not permitted during the study except during acute episodes such as hospitalization, trauma, or infection to manage glycemic control). [73]The dose and regimen of oral antidiabetic therapy could be changed to achieve glycemic control. However, initiation or uptitration of metformin was not permitted during the study due to the risk of lactic acidosis. If a patient experienced signs or symptoms of fluid-retention or an exacerbation of CHF, CHF medications could be adjusted by optimizing diuretic therapies, adjusting background ACEI/ARB therapy, adding cardiac glycosides, or the dose of *Avandia* could be reduced.

An independent committee conducted a blinded evaluation of fluid-related events (including CHF) and cardiovascular hospitalizations according to predefined criteria (adjudication).[73] Separate from the adjudication, other cardiovascular adverse events were reported by investigators. Although no treatment difference in change from baseline of ejection fractions was observed, more cardiovascular adverse events were observed with *Avandia* compared to placebo during the 52-week study (Table 5).

**Table 5. Emergent Cardiovascular Adverse Events (Study 211)[73]**

| | ***Avandia*** | **Placebo** | **P-value** |
|---|---|---|---|
| **EVENTS** | N = 110<br>n (%) | N = 114<br>n (%) | |
| **Major Adjudicated Clinical Endpoints** | | | |
| Cardiovascular Death | 5 (4.8) | 4 (3.8) | 0.85 |
| All-cause Mortality | 8 (7.7) | 5 (4.8) | 0.48 |
| All-cause Mortality or Worsening CHF | 11 (10.6) | 8 (7.5) | 0.59 |
| **Other Adjudicated Clinical Endpoints** | | | |
| Cardiovascular Hospitalization* | 21 (19.1) | 15 (13.2) | 0.47 |
| Definite Worsening CHF | 5 (4.5) | 4 (3.5) | 0.86 |
| Possible Worsening CHF | 2 (1.8) | 0 | N/A † |
| New or Worsening Edema | 28 (25.5) | 10 (8.8) | 0.01 |
| New or Worsening Dyspnea | 29 (26.4) | 19 (16.7) | 0.20 |
| Increase in CHF Medication | 36 (32.7) | 20 (17.5) | 0.04 |
| * Major reasons for cardiovascular hospitalization included worsening of CHF, myocardial infarction, and stroke/transient ischemic attack † No events occurred in one treatment group, preventing analysis using this model | | | |

***Reports of Macular Edema with Avandia***

Post-marketing reports of new-onset or worsening diabetic macular edema with decreased visual acuity have been reported with *Avandia*. Many of these patients reported concurrent peripheral edema. In some cases, the visual events resolved or improved following discontinuation of the drug.

**Background**

Macular edema typically occurs in association with diabetic retinopathy, although it is more likely to occur as retinopathy progresses. [74] Diabetic macular edema is a swelling of the retina that occurs after breakdown of the blood-retinal barrier because of leakage of dilated hyperpermeable capillaries and microaneurysms within the macula (the central portion of the retina. [75] Risk factors for macular edema include duration of diabetes, presence of retinopathy, hypertension, and poor glycemic control. [74] [75]

**Clinical Data**

In a retrospective chart review, Ryan et al identified 30 type 2 diabetic patients using a TZD who had both lower extremity edema that increased since starting the TZD and clinically significant macular edema.[76] Eleven patients received *Avandia*, 17 patients received Actos® (pioglitazone hydrochloride), and 2 patients received both TZDs at different times. Clinically significant macular edema was documented by clinical examination as well as review of color photographs and fluorescein angiograms. Fluid retention was noted to be present or absent. Response to TZD cessation was measured by reported weight loss, clinical estimation of lower extremity edema, visual acuity changes, and change in macular edema. Therapeutic

ocular intervention included focal laser treatment and therapeutic systemic intervention included TZD cessation, diuresis, and dialysis (1 case).

Of the 30 type 2 diabetes patients (average duration since diagnosis: 8.3 years), 23 patients also had hypertension, 6 patients had heart failure, and 1 patient had renal failure. [76] Additionally, 2 patients were on TZD monotherapy, 12 patients were receiving other oral antidiabetic medications with the TZD, 7 patients were receiving insulin in combination with the TZD, 7 patients were receiving other oral antidiabetic medications and insulin with the TZD, and 2 patients had no information available. Clinically significant macular edema was bilateral in 24 patients and unilateral in 6 patients. Macular laser photocoagulation was performed on 26 patients (48/60 eyes; ≥ 2 times in 22/60 eyes). Fluorescein angiography and clinical evaluation by a physician determined that the macular edema was diffuse in at least 1 eye of 19/30 patients, with 17/30 patients having bilateral diffuse macular edema. Average patient-reported weight gain while on the TZD was 23 lbs. Average patient-reported weight loss following TZD cessation was 19 lbs.

Decreased lower extremity edema was observed in all 11 patients followed for > 3 months after TZD cessation. [76] Ten of 11 patients also reported weight loss after TZD cessation. In these 11 patients, the average patient-reported weight gain was 30 lbs (range, 15-50 lbs) while on the TZD. The average patient-reported weight loss was 19 lbs (range 0-30 lbs) following TZD cessation. Of these 11 patients, 10 had hypertension, 3 developed renal failure, and 3 had heart failure. Reduction in macular edema occurred in < 3 months in 4/11 patients and in 8/11 patients over a 1- to 2-year period. These results should be interpreted with caution due to the retrospective nature of the analysis and the limitations inherent in such an analysis.

GlaxoSmithKline vigilantly monitors the safety of all of its products. As part of this monitoring, postmarketing reports of new onset or worsening (diabetic) macular edema have been received for some diabetic patients taking rosiglitazone or another thiazolidinedione (TZD). Some patients presented with blurred vision or decreased visual acuity, but some patients appear to have been diagnosed on routine ophthalmologic examination. Most patients had peripheral edema at the time macular edema was diagnosed. Some patients had improvement in their macular edema after discontinuation of their TZD. Patients with diabetes should have regular eye exams by an ophthalmologist, per the Standards of Care of the American Diabetes Association. Additionally, any diabetic patient who reports any kind of visual symptom should be promptly referred to an ophthalmologist, regardless of the patient's underlying medications or other physical findings[42].

***Avandia and Fractures***

**Background**

Over the last 20 years, data has been reported that indicates patients with type 2 diabetes are at increased risk of nonvertebral fracture, particularly fractures of the hip, arm and foot.[77,78,79,80] Elderly diabetic women are up to 6 times more likely to have a hip fracture than elderly nondiabetic women; the corresponding figure for elderly diabetic men is even higher (up to 8-fold higher risk).[81] The reason for this is unclear, particularly since type 2 diabetes tends to be associated with above average bone density and thus might be expected to be protective against osteoporosis and fracture.[80] Type 2 diabetes is known to be a predisposing factor for disability and falls in the elderly, and this predisposition has been postulated to account for some of the fractures.[82,83] However, even after adjusting for the frequency of falls, the fracture risk for diabetic patients persists.[80] Further information regarding fracture risk in type 2 diabetes is provided by analysis of data from the Women's Health Initiative Observational Study (WHIOS). [80] The WHIOS study enrolled a racially diverse group of over 93,000 postmenopausal women, collected detailed information on risk factors for fracture, and followed up this population for incident falls and fractures. A separate analysis of fracture data at various skeletal sites was conducted among the subgroup of 5,285 postmenopausal females (age 50-79 years; mean 64.9 years) with type 2 diabetes who participated in this study. Information on antidiabetic drug use in this patient population was limited to insulin, which was being taken by 17% of patients on study entry. Over the 7 year follow-up period, women with diabetes were 29% more likely to have a fracture of any type than women without diabetes.

**Clinical Information**

The ADOPT (A Diabetes Outcome Progression Trial) trial was designed to measure the long-term durability of glycemic control in people recently diagnosed with type 2 diabetes (≤3 years) receiving monotherapy with *Avandia* versus metformin or glyburide.(54) Among the 4,351 people with type 2 diabetes involved in ADOPT and treated for a median of 4 years, 200 people reported to experience at least one bone fracture event: 92 in the *Avandia* group (6.3% or 1.86 per 100 patient years); 59 in the metformin group (4.1% or 1.20 per 100 patient years) and 49 in the glyburide group (3.4% or 1.15 per 100 patient years).(84) The estimated hazard ratios [with 95% confidence interval (CI)] for the risk of fracture with *Avandia* versus metformin and glyburide were 1.57 (1.13, 2.17; $P = 0.0073$) and 1.61 (1.14, 2.28; $P = 0.0069$), respectively.

Men and women randomized to the three treatment groups were well matched at baseline.(84) The majority of women in the study were >50 years old (71%) and postmenopausal (77%) by self report. Please refer to Table 6. There were no clear differences in the pattern of use of concomitant medications, estrogen containing hormones, calcium supplements, bisphosphonates, thiazide and loop diuretics, or glucocorticoids, between women who did and did not report fracture within any treatment group.

**Table 6. Fracture Rates Reported in Women by Menopausal Status and Age(84)**

| | ***Avandia*** | | | **Metformin** | | | **Glyburide** | | |
|---|---|---|---|---|---|---|---|---|---|
| Pre-menopausal n† (%) | 10/147 (6.8) | | | 4/127 (3.2) | | | 3/156 (1.9)* | | |
| Post-menopausal n‡ (%) | 50/498 (10.0) | | | 26/463 (5.6)* | | | 18/449 (4.0)* | | |
| | With Fracture N = 60 | Without Fracture N = 585 | *P* Value | With Fracture N = 30 | Without Fracture N = 560 | *P* Value | With Fracture N = 21 | Without Fracture N = 584 | *P* Value |
| Age ≤ 50 n (%) | 11 (18.3) | 181 (30.9) | 0.065 | 8 (26.7) | 153 (27.3) | 0.954 | 3 (14.3) | 176 (30.1) | 0.012 |
| Age > 50 - ≤ 60 n (%) | 24 (40.0) | 205 (35.0) | | 11 (36.7) | 203 (36.3) | | 5 (23.8) | 197 (33.7) | |
| Age > 60 n (%) | 25 (41.7) | 199 (34.0) | | 11 (36.7) | 204 (36.4) | | 13 (61.9) | 211 (36.1) | |
| *$P < 0.05$ vs. *Avandia*; † n = number of premenopausal women that reported a fracture/total number of premenopausal women; ‡ n = number of postmenopausal women that reported a fracture/total number of postmenopausal women. | | | | | | | | | |

Of the 1,840 women in ADOPT, 111 experienced at least one bone fracture event, predominantly in the upper and lower limb.(84) These sites of fracture are different from those usually associated with postmenopausal osteoporosis (e.g., hip or spine). Of these, 60 women were in the *Avandia* group (9.3% or 2.74 per 100 patient years); 30 were in the metformin group (5.1% or 1.54 per 100 patient years) and 21 were in the glyburide group (3.5% or 1.29 per 100 patient years). The hazard ratios (with 95% CI) for the risk of fracture with *Avandia* versus metformin and glyburide in women were 1.81 (1.17, 2.80; $P = 0.008$) and 2.13 (1.30, 3.51; $P = 0.0029$), respectively. There was no increased risk of fracture with *Avandia* over the first 12 months of treatment, the increased risk manifested beyond 12 months of exposure. Amongst women that experienced a fracture event, 11.7%, 16.7%, and 23.8% reported accidental limb injury or fall within 30 days prior to the fracture and 18.3%, 16.7%, 14.3% reported more than one fracture in the *Avandia*, metformin, and glyburide groups, respectively. Please refer to Table 7. The observed fracture rates from ADOPT appear to be within the range seen in a literature based review of observational studies in women with diabetes and upon analysis of large managed care databases. (77,80,85,86)

There were no statistically significant differences observed among treatment groups in ADOPT in the number of fractures reported in men.(84) The hazard ratios for the risk of fracture with *Avandia* versus

metformin and glyburide in men were 1.18 (0.72, 1.96; $P = 0.5115$) and 1.08 (0.65, 1.79; $P = 0.7680$), respectively.

**Table 7. Patients with Fractures in ADOPT[84]**

| | ***Avandia*** | | **Metformin** | | **Glyburide** | |
|---|---|---|---|---|---|---|
| **MALE PATIENTS** | 811 Males | | 864 Males | | 836 Males | |
| | n (%) | Rate/100 PY | n (%) | Rate/100 PY | n (%) | Rate/100 PY |
| Experienced a fracture | 32 (4.0) | 1.16 | 29 (3.4) | 0.98 | 28 (3.4) | 1.07 |
| **FEMALE PATIENTS** | 645 Females | | 590 Females | | 605 Females | |
| | n (%) | Rate/100 PY | n (%) | Rate/100 PY | n (%) | Rate/100 PY |
| Experienced a fracture* | 60 (9.3) | 2.74 | 30 (5.1) | 1.54 | 21 (3.5) | 1.29 |
| *Lower limb*† | 36 (5.58) | 1.65 | 18 (3.05)§ | 0.92 | 8 (1.32)§ | 0.49 |
| Hip | 2 (0.31) | 0.09 | 2 (0.34) | 0.1 | 0 | 0 |
| Foot | 22 (3.41) | 1.01 | 7 (1.19)§ | 0.36 | 4 (0.66)§ | 0.25 |
| *Upper limb*‡ | 22 (3.41) | 1.01 | 10 (1.70) | 0.51 | 9 (1.49) | 0.55 |
| Hand | 8 (1.24) | 0.37 | 4 (0.68) | 0.21 | 1 (0.17) | 0.06 |
| Humerus | 5 (0.78) | 0.23 | 0 | 0 | 0 | 0 |
| Wrist | 5 (0.78) | 0.23 | 3 (0.51) | 0.15 | 4 (0.66) | 0.25 |
| *Spine* | 1 (0.16) | 0.05 | 1 (0.17) | 0.05 | 1 (0.17) | 0.06 |

* Some patients experienced fractures in more than one category; †Other sites of fracture included: ankle, femur, fibula, lower limb (general), patella, and tibia; ‡Other sites of fracture included: clavicle, forearm, radius, and upper limb (general).

n = number of patients; Rate/100 PY = Patients with events per 100 patient years.

§ $P < 0.05$ vs. *Avandia*

An independent safety committee reviewed an interim analysis of fractures in another large ongoing, long-term, controlled rosiglitazone clinical trial. The primary purpose of that study is to investigate cardiovascular endpoints in patients with type 2 diabetes mellitus. The results of the preliminary analysis were reported to GlaxoSmithKline as being consistent with the observations from ADOPT. The independent safety committee also recommended that the study continue without modification. Final results of this study are anticipated to be available in 2009.

**Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis**

Loke and colleagues assessed the risk of fractures in patients with impaired glucose tolerance (IGT) or type 2 diabetes with the long-term (≥ 1 year) use of thiazolidinediones (TZDs).[87] This analysis evaluated 10 randomized controlled trials (N = 13,715) and 2 observational studies (N = 31,679) through June 2008 that described the risk of fracture or change in bone density with TZDs. Long-term randomized controlled trials and observational studies that described the risk of fracture with any TZD (*Avandia*, pioglitazone, or troglitazone) were included in the analysis. The secondary outcome evaluated the effects of TZD therapy on bone mineral density (BMD). In this analysis, randomized controlled trials and observational studies of any duration that compared changes in bone mineral density in patients with and without TZD exposure were evaluated.

Pooled data from the 10 randomized controlled trials evaluated the risk of fractures associated with TZD therapy. As compared to the control, TZD therapy significantly increased the risk of overall fractures, (Odds Ratio[OR] 1.45, 95% Confidence Interval [CI] 1.18-1.79; $P < 0.001$) Additionally, data from 5 randomized trials reported that TZD therapy significantly increased the risk of fracture among women compared to control (OR 2.23, 95% CI 1.65-3.01; $P < 0.001$). Therapy with TZDs did not increase the risk of fracture risk among men (OR 1.00, 95% CI 0.73-1.39; $P = 0.98$).

A correlation between TZD exposure and fractures was also reported in 2 observational studies. A case-controlled study demonstrated a significant association between TZD exposure (current users with > eight prescriptions) and fractures among women (OR 2.56, 95% CI 1.43-4.58). Additionally, a separate cohort study reported that *Avandia* was significantly associated with fractures when compared to women taking metformin (OR 1.38, 95% CI 1.03-1.82). However, no greater fracture risk was seen in the comparison of *Avandia* and sulfonylurea (OR 0.89, 95% CI 0.69-1.14). In either study, there was no significant association with TZD exposure and fracturesamong men.

A change in BMD was identified in two randomized controlled trials and two observational studies. TZD therapy was associated with a consistent decline in BMD as compared with controls. A significant reduction in BMD at the lumbar spine and at the hip was observed among women who used TZD therapy. The percent change in BMD with weighted mean difference was -1.11% (95% CI -2.08 to -0.14%; $P$ = 0.02) and at the hip the weighted mean difference was -1.24% (95% CI -2.34% to -0.67%; $P < 0.001$.

The investigators interpretation of this data stated that long-term use of TZDs doubles the risk of fractures among women with type 2 diabetes, without a significant increase in risk of fractures among men with type 2 diabetes.

**Observational Study Exploring Fractures with Thiazolidinedione Use**

An observational, nested, case-controlled study in a UK-based general practice research database compared the risk of fractures in men and women with type 2 diabetes receiving thiazolidinediones (TZDs) to those on other oral antidiabetic drugs (OADs).[88] Between January 1994 and December 2005, individuals who received at least one prescription for a TZD, sulfonylurea, biguanide, alpha glucosidase inhibitor, or prandial glucose regulator, with or without concomitant insulin use (n = 50,048) and adults with type 2 diabetes who never received a prescription for an OAD or insulin (n = 16,648) were identified as study population. From this population, 1,020 patients with a first time diagnosis of low trauma fractures were identified and 3,728 control subjects without fracture diagnosis were randomly selected to match patients with fracture.

Clinically diagnosed low-trauma fractures consisted of wrist/forearm (301), hip (274), humerus (222), rib (148), vertebral (56) and others (19).[88] Of the 1,020 case patients with fracture, 65 subjects used thiazolidinediones (TZDs), all in combination with other oral antidiabetic drugs (OADs). After adjustments, including age, body mass index, other antidiabetic drugs, concomitant medications, and comorbidities, the odds ratio (OR) for current users of 8 or more TZD prescriptions, corresponding to 12-18 months of therapy, compared with non users was 2.43 [95% confidence interval (CI): 1.49 – 3.95]. The highest risk estimate was seen in users of 15 or more prescriptions, corresponding to 2 or more years of therapy [2.86 (95% CI: 1.57 - 5.22); $P < 0.001$]. The adjusted odds ratio on fracture risk for current users of 8 or more prescriptions of *Avandia* or pioglitazone was 2.38 (95% CI: 1.39 - 4.09) and 2.59 (95% CI: 0.96 - 7.01), respectively. In addition, the adjusted odds ratio for current users of 8 or more TZD prescriptions stratified by sex was 2.50 (95% CI 0.84-7.41) for men and 2.56 (95% CI 1.43-4.58) for women. In contrast to the observations in ADOPT (A Diabetes Outcome Progression Trial), risk of fracture also increased in men and TZD use was associated with an increased risk of hip and nonvertebral osteoporosis fractures in both men and women.

**4.12 Other Clinical Considerations**

***Avandaryl and Sulfa Allergy***

**Background**

The term "sulfa" historically refers to a derivative of the antimicrobial agent sulfanilamide, but more recently has been applied to a diverse group of drugs, all of which contain a sulfonamide chemical structure.[89] Sulfonamides are derivatives of sulfanilamide (para-aminobenzenesulfonamide) and contain an $SO_2NH_2$ moiety. This moiety is also part of many common medications. A sulfur dioxide and nitrogen moiety are directly linked to a benzene ring and are essential to the structure of sulfonamides.

An arylamine group at the $N^4$ position along the benzene ring is thought to be important to the development of hypersensitivity reactions. Sulfonamide-containing non-antibiotics, such as sulfonylureas and loop diuretics, do not possess this $N^4$ primary amine.[90]

**Clinical Information**

*Avandaryl* is contraindicated in patients with known hypersensitivity to this product or any of its components.[8] Although the rosiglitazone maleate component of *Avandaryl* contains a sulfur atom in its molecular structure, it is not related in structure to the sulfonamides, in that it does not contain a sulfonamide moiety ($SO_2NH_2$) that is characteristic to the structure of all sulfonamides. The molecular structure of the glimepiride component of *Avandaryl* contains a sulfonamide moiety ($SO_2NH_2$). An

arylamine at the $N^4$ position along the benzene ring may be structurally important to the development of a hypersensitivity reaction. Glimepiride does not contain an $N^4$ arylamine.

A retrospective cohort study conducted in the U.K. used a computerized General Practice Research Database of medical records to assess the risk of a subsequent allergic reaction to a sulfonamide nonantibiotic in patients that had a prior allergic reaction to sulfonamide antibiotics.(91) Secondary analyses also compared the risk of subsequent allergic reactions to penicillins in those patients with and without a prior allergic reaction after the initial receipt of a sulfonamide antibiotic. Patients were divided into 3 groups: source group, study group, and comparison group. The source group (n = 20,226) consisted of patients who received a systemic sulfonamide antibiotic and then received a prescription for a sulfonamide nonantibiotic within 60 days of the initial exposure to a sulfonamide antibiotic. Approximately 67% of the patients were female with nearly 40% being 65 years of age or older at the time of exposure. The study group (n = 969) consisted of patients from the source group who contacted their physician to report a condition consistent with an allergic reaction within 30 days of receiving a sulfonamide antibiotic. The comparison group (n = 19,257) consisted of those patients from the source group with no evidence of an allergic reaction within 30 days of exposure to the sulfonamide antibiotic. Glimepiride was included among the list of 38 sulfonamide nonantibiotics prescribed to patients. Allergic reactions were identified using a broad definition (e.g., asthma, eczema, and unspecified adverse events of the drug) and a narrow definition (e.g., urticaria, anaphylactic shock, erythema multiforme, and drug allergy).

Analysis of the medical records using the broad definition for allergic reaction showed that a total of 4.8% (969 of 20,226 patients) of the patients had an apparent allergic reaction within 30 days of receiving the initial sulfonamide antibiotic. Analysis based on the narrow definition yielded apparent allergic reactions in 0.4% (86 of 20,226 patients) of patients from the source group. Ninety-six (9.9%) of the 969 patients from the study group who had an allergic reaction to a sulfonamide antibiotic within 30 days had a subsequent reaction to a sulfonamide nonantibiotic. Three hundred-fifteen (1.6%) of the 19,257 patients from the comparison group who had no allergic reaction to a sulfonamide antibiotic had an allergic reaction after receiving a sulfonamide nonantibiotic (adjusted odds ratio 2.8; 95% confidence interval 2.1-3.7). However, the risk of an allergic reaction was greater after the receipt of penicillin in those patients with a prior reaction to a sulfonamide antibiotic compared to those without such a reaction (adjusted odds ratio 3.9; 95% confidence interval 3.5-4.3). A total of 9.7% (40 of 411) of patients that experienced an allergic reaction after receiving a sulfonamide nonantibiotic required hospitalization. The most common diagnoses used to identify allergic reactions in this study were asthma (70.1%), eczema (14.1%) and adverse drug reaction (11.4%).

According to the investigators, these results suggest that allergy to a sulfonamide antibiotic is a risk factor for a subsequent allergic reaction to a sulfonamide nonantibiotic and a penicllin allergy is at least as strong a risk factor. These associated risks for allergic reactions may be due to a predisposition to allergic reactions rather than to cross-reactivity with sulfonamide-based medications.

### 4.13 Drug/Food/Disease Interactions

Refer to Enclosed Prescribing Information.

### 4.14 Dosing and Administration

Refer to Enclosed Prescribing Information.

## 5. EFFICACY AND SAFETY TRIALS (FDA APPROVED)

### 5.1 Efficacy and Safety of *Avandia* Add-on Therapy to a Sulfonylurea in the Treatment of Type 2 Diabetes

#### *Avandia* Add-on Therapy to a Sulfonylurea

The safety and efficacy of *Avandia* added to a sulfonylurea has been studied in clinical trials in patients with type 2 diabetes inadequately controlled on sulfonylureas alone. No clinical trials have been conducted with the fixed-dose combination tablet *Avandaryl* as a second-line therapy (i.e., in patients inadequately controlled on sulfonylurea or who have initially responded to *Avandia* alone and require additional glycemic control).

A total of 3,457 patients with type 2 diabetes participated in ten 24 to 26 week randomized, double blind, placebo/active controlled studies and one 2-year double-blind, active-controlled study in elderly patients designed to assess the efficacy and safety of *Avandia* in combination with a sulfonylurea.[52,57,58,59,60,61,62,63,64,65,69] *Avandia* 2 mg, 4 mg, or 8 mg daily, was administered either once daily (3 studies) or in divided doses twice daily (7 studies), to patients inadequately controlled on a submaximal or maximal dose of sulfonylurea. In these studies, the combination of *Avandia* 4 mg or 8 mg daily (administered as single or twice daily divided doses) and a sulfonylurea significantly reduced fasting plasma glucose (FPG) and HbA1c compared to placebo plus sulfonylurea or further up titration of the sulfonylurea. Table 8 and Table 9 show pooled data for 8 studies in which *Avandia* added to sulfonylurea was compared to placebo plus sulfonylurea.

**Table 8. Effects of Twice Daily *Avandia* Plus a Sulfonylurea on FPG and HbA1c in 24- to 26- Week Combination Studies[58,59,61,64,65]**

| **Twice Daily Divided Dosing (5 studies)** | **Sulfonylurea** | ***Avandia* 2 mg twice daily + sulfonylurea** | **Sulfonylurea** | ***Avandia* 4 mg twice daily + sulfonylurea** |
|---|---|---|---|---|
| N | 397 | 497 | 248 | 346 |
| FPG (mg/dL) | | | | |
| Baseline (mean) | 204 | 198 | 188 | 187 |
| Change from baseline (mean) | 11 | -29 | 8 | -43 |
| Difference from sulfonylurea alone (adjusted mean) | - | -42* | - | -53* |
| % of patients with ≥30 mg/dL decrease from baseline | 17% | 49% | 15% | 61% |
| HbA1c | | | | |
| Baseline (mean) | 9.4 | 9.5 | 9.3 | 9.6 |
| Change from baseline (mean) | 0.2 | -1.0 | 0.0 | -1.6 |
| Difference from sulfonylurea alone (adjusted mean) | - | -1.1* | - | -1.4* |
| % of patients with ≥0.7% decrease from baseline | 21% | 60% | 23% | 75% |
| * $P \leq 0.0001$ compared to sulfonylurea alone. | | | | |

**Table 9. Effects of Once Daily *Avandia* Plus a Sulfonylurea on FPG and HbA1c in 24- to 26- Week Combination Studies[57,63,69]**

| Once Daily Dosing (3 studies) | Sulfonylurea | *Avandia* 4 mg once daily + sulfonylurea | Sulfonylurea | *Avandia* 8 mg once daily + sulfonylurea |
|---|---|---|---|---|
| N | 172 | 172 | 173 | 176 |
| FPG (mg/dL) | | | | |
| Baseline (mean) | 198 | 206 | 188 | 192 |
| Change from baseline (mean) | 17 | -25 | 17 | -43 |
| Difference from sulfonylurea alone (adjusted mean) | - | -47* | - | -66* |
| % of patients with ≥30 mg/dL decrease from baseline | 17% | 48% | 19% | 55% |
| HbA1c (%) | | | | |
| Baseline (mean) | 8.6 | 8.8 | 8.9 | 8.9 |
| Change from baseline (mean) | 0.4 | -0.5 | 0.1 | -1.2 |
| Difference from sulfonylurea alone (adjusted mean) | - | -0.9* | - | -1.4* |
| % of patients with ≥0.7% decrease from baseline | 11% | 36% | 20% | 68% |
| * $P \leq 0.0001$ compared to sulfonylurea alone. | | | | |

One of the 24 to 26 week studies included patients who were inadequately controlled on maximal doses of glyburide and switched to *Avandia* 4 mg daily as monotherapy; in this group, loss of glycemic control was demonstrated, as evidenced by increases in FPG and HbA1c.[58]

Pooled results (Studies 127, 132, 143, 145, 147, 162, 015, 079, 096) of on-therapy adverse events occurring in >3% of patients in any treatment group during the 24- to 26-week studies in which *Avandia* was added to sulfonylurea therapy are presented in Table 10.

**Table 10. Pooled Adverse Events from Nine 24- to 26-week *Avandia* Plus Sulfonylurea Combination Studies[57,58,59,60,61,62,63,64,65]**

| | *Avandia* 4 mg/day + Sulfonylurea N = 622 | *Avandia* 8 mg/day + Sulfonylurea N = 885 | Sulfonylurea N = 1213 |
|---|---|---|---|
| Preferred Term | % | % | % |
| Edema* | 7.4 | 12.4 | 1.6 |
| Hypoglycemia | 6.6 | 11.8 | 3.1 |
| Weight Increase | 4.3 | 9.6 | 1.0 |
| Pain† | 3.5 | 6.8 | 5.7 |
| URTI | 11.6 | 7.1 | 7.0 |
| Urinary Tract Infection | 6.1 | 4.4 | 3.3 |
| Hyperlipemia | 4.8 | 4.2 | 0.7 |
| Injury‡ | 4.7 | 3.8 | 5.0 |
| Dizziness | 4.8 | 3.4 | 2.8 |
| Anemia | 1.3 | 3.1 | 0.7 |
| Arthralgia | 3.4 | 2.9 | 1.9 |
| *Edema includes edema dependent, edema legs, edema peripheral, and edema generalized; † Pain includes pain and back pain; ‡ Injury includes items such as cuts, burns, sprains, fractures, accidents, and surgical procedures. URTI = Upper respiratory tract infection. | | | |

| | ***Avandia* 4 mg/day + Sulfonylurea N = 622** | ***Avandia* 8 mg/day + Sulfonylurea N = 885** | **Sulfonylurea N = 1213** |
|---|---|---|---|
| Headache | 4.0 | 2.7 | 4.5 |
| Hypercholesterolemia | 3.7 | 2.6 | 0.9 |
| Hyperglycemia | 2.7 | 0.5 | 6.1 |
| *Edema includes edema dependent, edema legs, edema peripheral, and edema generalized; † Pain includes pain and back pain; ‡ Injury includes items such as cuts, burns, sprains, fractures, accidents, and surgical procedures.<br>URTI = Upper respiratory tract infection. | | | |

As part of its ongoing monitoring and assessment of the safety of *Avandia*, GlaxoSmithKline proactively conducted a series of retrospective analyses to characterize the degree of association, if any, between *Avandia* and events of congestive heart failure (CHF) and myocardial ischemia.[92] Forty-two controlled and blinded clinical trials in which 4 mg or 8 mg doses of *Avandia* was used were included in the analysis. Observations regarding CHF and *Avandia* therapy remain consistent with reports and observations from individual and integrated controlled clinical trials of an increased incidence of CHF in patients treated with *Avandia* and sulfonylurea combinations.

**Study 325**

A 24-week, randomized, double-blind, placebo-controlled study (Study 325) evaluated the efficacy and safety of *Avandia* in combination with submaximal therapeutic doses of glimepiride in 391 patients with type 2 diabetes inadequately controlled on non-thiazolidinedione oral antidiabetic monotherapy.[66] During a 6-week run-in period patients discontinued their current antidiabetic medication and received glimepiride 2 mg/day plus placebo. All patients were randomized to receive *Avandia* 4 mg/day plus glimepiride 2 mg/day (titratable to 4 mg/day after 8 weeks) or glimepiride 4 mg/day (titratable to 8 mg/day after 8 weeks) plus placebo for 24 weeks. The primary efficacy parameter of the study was change in HbA1c from baseline to week 24. Results are presented in Table 11.

**Table 11. Evaluation of *Avandia* in Combination with Glimepiride vs Uptitrated Glimepiride[66]**

| **Study Design/ Mean Baseline Characteristics** | **Regimen** | **Baseline HbA1c (%)/FPG (mg/dL)** | **Primary Endpoint HbA1c (%)** | | **Secondary Endpoint FPG (mg/dL)** | |
|---|---|---|---|---|---|---|
| R, DB, PC<br>24 weeks<br>Age 53.5 yrs<br>56.6% male | Intent-to-treat population | | Mean Difference from Baseline | Mean Difference from glimepiride + placebo | Mean Difference from Baseline | Mean Difference from glimepiride + placebo |
| | n = 181<br>*Avandia* 4 mg QD + glimepiride | 8.15/190.9 | -0.68* | -0.56† | -27.7* | -24.5† |
| | n = 181<br>glimepiride + placebo | 8.01/183.6 | -0.08 | - | -0.6 | - |
| * Significant change vs. baseline ($P < 0.0001$); † Significant vs. glimepiride + placebo ($P < 0.0001$).<br>DB = Double-blind; FPG = Fasting plasma glucose; HbA1c = glycosylated hemoglobin; PC = Placebo-controlled; QD = Once daily; R = Randomized. | | | | | | |

Overall, the most common adverse events (> 4%) reported among all randomized patients were hypoglycemia (*Avandia* + glimepiride 20.9%; glimepiride + placebo 13.3%), nasopharyngitis (*Avandia* + glimepiride 5.1%; glimepiride + placebo 9.7% and peripheral edema (*Avandia* + glimepiride 4.1%; glimepiride + placebo 5.6%).[66] One patient in the glimepiride + placebo uptitration group withdrew

due to severe hypoglycemia. Weight gain was reported by 3.6% of patients treated with *Avandia* plus glimepiride and 0.5% of patients treated with glimepiride plus placebo.

### 5.2 Efficacy and Safety of *Avandaryl* in Drug-Naïve Patients with Type 2 Diabetes

#### Clinical Information

A 28-week, multicenter, randomized, double-blind, parallel-group study compared the efficacy and safety of treatment with *Avandaryl* to glimepiride monotherapy and rosiglitazone maleate monotherapy in 901 drug-naïve subjects with type 2 diabetes mellitus.[10] The objective of this study was to evaluate the effects of treatment of two *Avandaryl* regimens when compared to glimepiride and rosiglitazone maleate monotherapies, with respect to mean change from baseline in HbA1c, after 28 weeks of treatment.

To be eligible for the study, male and female subjects had to be 18 to 75 years of age with type 2 diabetes and a screening HbA1c of 7.5% to 12.0%, fasting C-peptide ≥0.8 ng/mL, and fasting plasma glucose (FPG) ≥126 mg/dL.[10] Among the reasons for exclusion from participation in the study was a history of severe hypoglycemia, severe edema, or prior history of severe edema, prior history of hepatocellular reaction, clinically significant hepatic or renal disease, anemia, uncontrolled hypertension, unstable or severe angina, or congestive heart failure requiring pharmacological treatment. In Europe the exclusion criteria with regard to heart failure excluded subjects from participation if they were known to have New York Heart Association (NYHA) class I-IV heart failure.[93] All antidiabetic medications (e.g., oral antidiabetic medication [OAD], insulin) other than study medications were prohibited during the study. The use of OAD or insulin for more than 15 days within 4 months prior to screening medication was prohibited and subjects were excluded from participation in the study. Subjects who used OADs or insulin for less than 15 days were screened for the study, provided at least 2 weeks had elapsed between their last dose of medication and the screening date.

The study was comprised of four treatment groups: glimepiride monotherapy, rosiglitazone monotherapy, and two *Avandaryl* groups and consisted of a 2-week screening period and a 28-week treatment period.[10] Randomization was stratified according to screening HbA1c (HbA1c >7.5% to ≤9.5%; >9.5% to ≤12%) and gender. During the treatment period, a subjects' dose level was increased at Weeks 4, 8, and 12 unless their mean daily glucose (MDG) was below 110 mg/dL. Subjects who reported frequent or severe hypoglycemia were continued at the current dose level or decreased their dose level, according to the investigator's discretion. Subjects were discontinued from the study in those instances where a confirmatory FPG measurement was ≥240 mg/dL and where study medication was administered at the highest tolerated dosage level for at least four weeks. At baseline (Visit 2, week 0), eligible subjects were randomized to one of the following treatment groups:

- Glimepiride monotherapy: subjects began taking glimepiride 1mg once daily (OD) and the dose could be titrated to a maximum of 4mg OD.
- Rosiglitazone monotherapy: subjects began taking rosiglitazone 4mg OD and the dose could be titrated to a maximum of 8mg OD.
- *Avandaryl* Regimen A: subjects began taking rosiglitazone 4mg/glimepiride 1mg OD and the dose could be titrated to a maximum of 4mg/4mg OD.
- *Avandaryl* Regimen B: subjects began taking rosiglitazone 4mg/glimepiride 1mg OD and the doses could be titrated to a maximum dose of 8mg/4mg OD.

Demographic and baseline disease characteristics were similar across treatment groups.[10] Subjects were generally obese (approximate mean body mass index 32kg/m$^2$) and had a mean age of approximately 54 years. The majority of subjects were white (77%) and male (59%). The median duration of diabetes was 1-2 years across groups. At baseline (Week 0), mean HbA1c was 9.0-9.2% and mean FPG was 206.9-214.1 mg/dL across treatment groups, respectively. The most frequently reported current medical conditions were hypertension and dyslipidemia.

The primary efficacy endpoint was change in HbA1c from baseline to Week 28 of double-blind treatment.[10] Secondary efficacy endpoints included change in FPG from baseline to Week 28 of double-blind treatment and percent change in homeostasis model assessment – insulin sensitivity (HOMA-S) and homeostasis model assessment – beta cell function (HOMA-B) from baseline to Week 28 of double-blind treatment. The primary efficacy analysis showed that mean HbA1c decreased from

baseline to Week 28 in each treatment group with greater reductions in the *Avandaryl* Regimen A and *Avandaryl* Regimen B groups: glimepiride monotherapy= -1.72%, rosiglitazone monotherapy = -1.75%, *Avandaryl* Regimen A = -2.41% and *Avandaryl* Regimen B = -2.52%. The adjusted mean treatment difference for the change from baseline in HbA1c was statistically greater for *Avandaryl* Regimen A and *Avandaryl* Regimen B treatment compared to glimepiride ($P < 0.0001$) and rosiglitazone ($P < 0.0001$) monotherapies. Please refer to Table 1.

The decrease in mean HbA1c was observed as early as Week 4, the first on-therapy HbA1c assessment, and continued to decline through the end of treatment with statistically greater reductions in the *Avandaryl* Regimen A and *Avandaryl* Regimen B groups at Week 28.[10,93] A greater percentage of subjects in the *Avandaryl* Regimen A and Regimen B groups achieved the American Diabetes Association (ADA) HbA1c target of <7.0% [*Avandaryl* Regimen A 75%, *Avandaryl* Regimen B 72%, glimepiride monotherapy 49% and rosiglitazone monotherapy 46%] and the American Association of Clinical Endocrinologists (AACE) HbA1c target of ≤6.5% [*Avandaryl* Regimen A 56%, *Avandaryl* Regimen B 54%, glimepiride monotherapy 32% and rosiglitazone monotherapy 31%]. The odds ratios were statistically significant in favor of both *Avandaryl* Regimen A and Regimen B treatment groups compared with glimepiride and rosiglitazone monotherapies ($P < 0.0001$ for each combination therapy group versus each monotherapy group).

**Table 12. Change in HbA1c from Baseline to Week 28 (ITT with LOCF) [10,93]**

| **HbA1c (%)** | **GLIM n = 218** | **RSG n = 225** | ***Avandaryl* Regimen A n = 221** | ***Avandaryl* Regimen B n = 210** |
|---|---|---|---|---|
| Baseline (mean) | 8.96 | 9.13 | 9.02 | 9.16 |
| Δ from Baseline (mean) | -1.72 | -1.75 | -2.41 | -2.52 |
| Difference from GLIM*(mean) | | | -0.63† | -0.66† |
| Difference from RSG*(mean) | | | -0.73† | -0.77† |
| * Based on analysis of covariance: change = baseline + treatment + country + gender; GLIM = glimepiride monotherapy treatment group; † $P < 0.0001$; ITT = intent-to-treat; LOCF = last observation carried forward; n = number of subjects with a baseline and on-therapy value; RSG = rosiglitazone monotherapy treatment group. | | | | |

Mean FPG decreased from baseline to Week 28 in each treatment group with greater reductions in the *Avandaryl* Regimen A and *Avandaryl* Regimen B groups: GLIM=-42.2mg/dL, RSG =-56.6mg/dL, *Avandaryl* Regimen A=-69.5mg/dL, and *Avandaryl* Regimen B=-79.9mg/dL.[10] The adjusted mean treatment difference for the change in FPG was statistically greater for the *Avandaryl* Regimen A and *Avandaryl* Regimen B treatment compared to GLIM ($P <0.0001$) and RSG ($P <0.0001$) monotherapies. Please refer to Table 2. A reduction in mean FPG was observed as early as Week 2 in the *Avandaryl* treatment groups, the first on-therapy visit, and continued to decline through the end of treatment.[10,93]

**Table 13. Change in FPG from Baseline to Week 28 (ITT with LOCF) [10,93]**

| FPG (mg/dL) | GLIM n = 221 | RSG n = 225 | *Avandaryl* Regimen A n = 219 | *Avandaryl* Regimen B n = 213 |
|---|---|---|---|---|
| Baseline (mean) | 211.2 | 211.9 | 206.9 | 213.5 |
| Δ from Baseline (mean) | -42.2 | -56.6 | -69.5 | -79.9 |
| Difference from GLIM*(mean) | | | -30.0† | -36.9† |
| Difference from RSG*(mean) | | | -15.9† | -22.8† |

*Based on analysis of covariance: change = baseline + treatment + country + gender + screening HbA1c; † $P <$ 0.0001; FPG = fasting plasma glucose; GLIM = glimepiride monotherapy treatment group; ITT = intent-to-treat; LOCF = last observation carried forward; n = number of subjects with a baseline and on-therapy value; RSG = rosiglitazone monotherapy treatment group.

At study end, the majority of subjects in the monotherapy groups were up-titrated to the maximum dose (glimepiride monotherapy: 67%, rosiglitazone monotherapy: 77%) compared with approximately half the subjects in the *Avandaryl* Regimens (*Avandaryl* Regimen A: 47%, *Avandaryl* Regimen B: 54%).[10]

Both of the *Avandaryl* Regimens were generally well tolerated with the adverse event (AE) profiles similar to the rosiglitazone and glimepiride monotherapy regimens.[10] The most commonly reported AEs were headache (approximately 4.4%) and nasopharyngitis (approximately 4.4%).

Hypoglycemia was reported separately from other AEs and was based on symptoms and/or a blood glucose reading of <50 mg/dL.[10,93] The percentage of subjects with confirmed hypoglycemia (symptoms plus fingerstick glucose <50 mg/dL) was 4.1% in the glimepiride monotherapy group, 0.4% in the rosiglitazone monotherapy group, 3.6% in the *Avandaryl* Regimen A group, and 5.5% in the *Avandaryl* Regimen B group.[10] No hypoglycemic events were reported as serious AEs and no subjects were withdrawn from the study due to hypoglycemia.

Overall, 1.1% of subjects reported treatment-related weight gain.[10] Treatment-related weight gain was not reported as an AE in individuals receiving glimepiride monotherapy, but was reported in 0.4% of subjects receiving rosiglitazone monotherapy, 3.1% of subjects receiving *Avandaryl* Regimen A, and 3.2% of subjects receiving *Avandaryl* Regimen B. The median increases in weight from baseline (25th, 75th percentile) were 1.10 kg (-1.20, 3.30) for glimepiride monotherapy, 1.00 kg (-1.00, 3.55) for rosiglitazone monotherapy, 2.00 kg (0.00, 4.60) for *Avandaryl* Regimen A, and 3.40 kg (0.45, 6.30) for *Avandaryl* Regimen B.

In all groups, the incidence of anemia was low and there were no withdrawals due to anemia (0% for glimepiride monotherapy group, 2.2% for rosiglitazone monotherapy group, 0.9% for *Avandaryl* Regimen A group, and 1.8% for *Avandaryl* Regimen B group).[10] Edema was reported in 2.3%, 3.0%, 2.7%, and 3.2% of subjects in the glimepiride monotherapy, rosiglitazone monotherapy, *Avandaryl* Regimen A, and *Avandaryl* Regimen B groups, respectively.

Cardiac ischemic events were reported by 7 subjects (0.9%, 1.3%, 0.4% and 0.5% in the rosiglitazone monotherapy group, glimepiride monotherapy group, *Avandaryl* Regimen A group, and *Avandaryl* Regimen B group, respectively).[10] One of these events in the glimepiride monotherapy group and 2 in the rosiglitazone monotherapy group were reported as serious AEs and occurred in subjects who had a prior history of coronary heart disease. One subject in the rosiglitazone monotherapy group and one in the *Avandaryl* Regimen B group experienced congestive heart failure.

## 6. ADDITIONAL SAFETY INFORMATION

### 6.1 Interim Analysis of the RECORD Study

**RECORD**

RECORD (*R*osiglitazone *E*valuated for *C*ardiac *O*utcomes and *R*egulation of glycemia in *D*iabetes), a long-term, randomized, multicenter, open-label, noninferiority study in type 2 diabetes patients, was initiated by GlaxoSmithKline in 2000. [56,94] The study was designed to prospectively compare cardiovascular outcomes in patients with type 2 diabetes treated with *Avandia* plus metformin or sulfonylurea (*Avandia* group) with outcomes in patients treated with metformin plus sulfonylurea (control group).

This study included 4447 type 2 diabetes patients with a HbA1c > 7% and ≤9% despite maximum doses of a sulfonylurea or metformin alone from 338 European and Australian study centers.[56] After a 4 week run-in, patients who were already taking a sulfonylurea were randomly assigned to receive the addition of either *Avandia* (n=1103) or metformin (n=1122). Patients who were already taking metformin were randomly assigned to receive the addition of either *Avandia* (n=1117) or a sulfonylurea (n=1105). The starting dose of *Avandia* was 4 mg/day and the starting doses of metformin and sulfonylurea were determined by local practice. Throughout the study, medications were titrated (following 8 weeks of treatment) to achieve a target HbA1c of ≤ 7%. The maximum daily dose of *Avandia* was 8 mg/day and the maximum dose of metformin was 2550 mg/day. The maximum dose of sulfonylurea was 15 mg/day for glyburide, 240 mg/day for gliclazide, and 4 mg/day for glimepiride. If HbA1c remained ≥ 8.5%, a third oral antidiabetic agent was added in the *Avandia* group or insulin was added in the control group. Patients in the control group (metformin plus sulfonylurea) who started insulin did so according to local practice with or without continuing metformin and/or sulfonylurea. [94] If patients receiving triple therapy in the *Avandia* group had a HbA1c ≥ 8.5%, the study protocol recommended discontinuation of *Avandia* and initiation of insulin. Patients will be followed for approximately 6 years with an anticipated study completion date of late 2008.

The primary endpoint of the study was cardiovascular (CV) hospitalization or death.[56] CV hospitalizations included hospitalization for acute myocardial infarction, congestive heart failure (CHF), stroke, unstable angina, transient ischemic attack, unplanned CV revascularization, amputation of extremities, or any other definite CV reason. CV death included death from CHF, acute myocardial infarction, sudden death, and death caused by acute vascular events such as stroke. Secondary outcomes included all-cause mortality, CHF, combined CV death and/or hospitalization plus microvascular endpoints, all microvascular endpoints, progression of glucose control and need for insulin. [94] An interim analysis of the glycemic control outcomes at 18 months has been published for RECORD.[95] Safety evaluations included monitoring of changes in physical examination, vital signs, laboratory tests, adverse events, and electrocardiograms.

A meta-analysis published in the *New England Journal of Medicine* raised concern regarding the risk of myocardial infarction and CV death associated with *Avandia*. To provide additional information regarding the CV safety of *Avandia*, an unplanned interim analysis was conducted to evaluate the CV outcomes reported so far in the RECORD study. [56] Results of this interim analysis study were published in the *New England Journal of Medicine* on June 5, 2007.

In the RECORD study, there were 2220 patients assigned to receive *Avandia* added to metformin or sulfonylurea (*Avandia* group), and 2227 were assigned to receive a combination of metformin plus a sulfonylurea (control group).[56] The protocol excluded some high-risk patients (i.e. those with CHF, hospitalization for CV causes during the previous 3 months, and pending CV intervention). Baseline characteristics were similar between treatment groups. A total of 140 patients in the *Avandia* group and 244 patients in the control group began to receive insulin. Approximately 10% of patients (218 in the *Avandia* group and 223 in the control group) were lost to follow-up. The interim analysis of RECORD had limited statistical power to detect treatment differences because of the number of patients lost to follow-up, because there was a much lower overall event rate than predicted, and because the mean follow-up was only 3.75 years. Due to the limited power of the interim analysis, a conclusion on the primary endpoint must await the completion of the study.

There was no significant difference between the *Avandia* group and the control group in the adjudicated primary endpoint of CV hospitalization and death. [56] A total of 217 patients in the *Avandia* group and 202 patients in the control group experienced the adjudicated primary endpoint (hazard ratio, 1.08; 95% confidence interval [CI], 0.89 to 1.31). After the inclusion of endpoints for an additional 91 patients (50 in the *Avandia* group and 41 in the control group) pending adjudication, the hazard ratio was 1.11

(95% CI, 0.93 to 1.32). Overall, the rate of the primary endpoint (CV hospitalization or death) was low: 3.1% per year for adjudicated plus pending events.

For the secondary endpoints of myocardial infarction, death from CV or any cause (total mortality), or the composite of CV death, myocardial infarction, and stroke, hereafter referred to as major adverse cardiovascular events (MACE), there was no statistically significant differences between the *Avandia* group and the control group. [56] See Table 14. At this point, the data do not allow a conclusion on the relative risk of myocardial infarction among the medications studied.

**Table 14. Hazard Ratios for the Risk of MACE, Myocardial Infarction, and Total Mortality[96]**

| | MACE | | Myocardial Infarction* | | Total Mortality | |
|---|---|---|---|---|---|---|
| | n (%) | HR (95% CI) | n (%) | HR (95% CI) | n (%) | HR (95% CI) |
| RSG + SU or MET N = 2220 | 93 (4.2) | 0.97 (0.73, 1.28) | 49 (2.2) | 1.09 (0.73, 1.63) | 74 (3.3) | 0.92 (0.67, 1.26) |
| SU + MET N = 2227 | 96 (4.3) | | 45 (2.0) | | 80 (3.6) | |

* Myocardial infarction or sudden death.
MACE = major adverse cardiovascular events; HR = hazard ratio; CI = confidence interval; RSG = rosiglitazone; SU = sulfonylurea; MET = metformin

Regarding stroke, a post-study ad hoc analysis indicated no statistically significant differences between the *Avandia* group (n = 2220) and the control group (n = 2227) with regard to rate of events per 100 patient-years ( 0.35 versus 0.46, respectively). [96] The risk of stroke was 24% lower in the *Avandia* group as compared with control (HR 0.76: 0.47-1.23).

Patients in the *Avandia* group had a significantly higher risk of CHF than did patients in the control group, with 38 versus 17 adjudicated events (hazard ratio, 2.24; 95% CI, 1.27 to 3.97). [56] The inclusion of events pending adjudication increased the number of events to 47 and 22, respectively (hazard ratio, 2.15; 95% CI, 1.30 to 3.57), resulting in an excess risk of CHF in the *Avandia* group of 3.0 (95% CI, 1.0 to 5.0) per 1000 patient years of follow-up.

In summary, a significant difference between the *Avandia* and control groups was seen only in the secondary outcome of CHF, where more than twice the number of cases were seen in patients treated with *Avandia*. [56] An independent data safety monitoring board which monitors unblinded safety data twice annually and monitors outcomes throughout the course of the study, has recommended that the RECORD study continue following the interim analysis.

## 7. COMPARATIVE DATA

### 7.1 Results of the ADOPT Trial

*A D*iabetes *O*utcome *P*rogression *T*rial (ADOPT) was an international, multicenter, randomized, double-blind controlled clinical trial involving 4,360 patients with a median treatment of 4 years.[54] ADOPT was conducted to evaluate the durability of glycemic control in recently diagnosed (<3 years) type 2 diabetes patients receiving *Avandia*, metformin, or glyburide monotherapy. The primary outcome was the time to monotherapy failure, defined as confirmed hyperglycemia when fasting plasma glucose (FPG) > 180 mg/dl on consecutive testing after at least 6 weeks of treatment at the maximal effective or tolerated dose.[54,97] The therapeutic goal was a FPG < 140mg/dl. Fasting plasma glucose values used within the study protocol are consistent with treatment guidelines during the period of study enrollment.

A total of 6,676 patients was screened of which 4,351 were randomized to receive either *Avandia* (n = 1456), metformin (n=1454), or glyburide (n = 1441).[54] Eligible participants randomized for the trial were between the ages of 30 and 75 years, had an FPG that was between 126-180 mg/dl, and had received no prior pharmacologic treatment for their type 2 diabetes; the disease had previously only been managed with diet and exercise. Of those randomized, the majority of participants were male (57.7%), with a

mean age and body mass index (BMI) of 56.9 years and 32.2, respectively. Participants with a history of clinically significant hepatic disease, renal impairment, lactic acidosis, unstable or severe angina, congestive heart failure (CHF) New York Heart Association Class I-IV, or uncontrolled hypertension were excluded from participation in the trial.

A placebo run-in of 4 weeks was followed by a median treatment duration of 4 years (maximum 6 years).[54,97] Participants were randomized initially to receive a total daily dose of *Avandia* 4mg, metformin 500mg, or glyburide 2.5mg.[54] During the treatment period, up-titration occurred during each study visit if FPG ≥ 140 mg/dl to a maximum daily dose of *Avandia* 8mg, metformin 2g, and glyburide 15mg. Dose reduction was permitted if study medication was not tolerated. Participants who withdrew from the study prior to completion were given the option to enter a non-treatment observational follow-up.

The primary outcome was the time from randomization to monotherapy treatment failure. Treatment failure was defined as:

- Confirmed hyperglycemia (FPG > 180mg/dl) on consecutive testing after at least 6 weeks of treatment at the maximum tolerated or dictated dose.

An independent adjudication committee used criteria to determine whether the primary outcome had been met in cases where a confirmatory FPG had not been obtained, a patient had withdrawn due to insufficient therapeutic effect, or an additional glucose lowering agent had been administered prior to confirmed hyperglycemia.

Secondary outcomes included time from randomization to a confirmed FPG > 140mg/dl after at least 6 weeks of treatment at the maximum tolerated dose of study medication.

Other prespecified secondary outcomes included:

- FPG
- A1C
- Measures of estimates of insulin sensitivity and β-cell function
- Weight

The primary comparisons within the ADOPT trial were *Avandia* versus metformin and *Avandia* versus glyburide. Secondary analysis was conducted to compare metformin and glyburide.

The cumulative incidence of monotherapy failure at 5 years, according to Kaplan-Meier analysis, was 15% with *Avandia*, 21% with metformin, and 34% with glyburide.[54] This represents a 32% risk reduction in the primary outcome of time to progression to monotherapy failure with *Avandia* as compared with metformin [95% Confidence Interval (CI) 15-45%; $P < 0.001$)], and a 63% risk reduction with *Avandia* as compared with glyburide [95% CI 55-70%; $P < 0.001$]. Additionally, as compared with glyburide, metformin was associated with a 46% risk reduction [95% CI 36-55%, $P < 0.001$] in the primary outcome of time to progression of monotherapy failure. At the time of treatment failure, 99.3 % of participants in the *Avandia* group, 98.6% in the metformin group, and 99.0% in the glyburide group were receiving the maximum dose of study medication. Findings with regard to treatment failure not requiring adjudication remained consistent with those of the primary outcome. A 31% risk reduction in the primary outcome of time to progression to monotherapy failure with *Avandia* as compared with metformin [95% Confidence Interval (CI) 11-46%; $P = 0.004$)], and a 66% risk reduction with *Avandia* as compared with glyburide [95% CI 57-73%; $P < 0.001$] was reported for non-adjudicated treatment failures. Subgroup analyses indicated that *Avandia* was more effective than glyburide in all subgroups while a greater treatment effect was seen with *Avandia* as compared with metformin among older participants ( ≥ 50 yrs) [*P*-value for heterogeneity = 0.03] and those with larger waist circumference (>110cm) [*P*-value for heterogeneity = 0.01].

There was a 36% risk reduction in the secondary outcome of time to progression to FPG > 140mg/dl with *Avandia* as compared with metformin [79/511 and 127/520, respectively; 95% CI 15-52%; $P = 0.002$] and a 62% risk reduction with *Avandia* as compared with glyburide [79/511 and 160/480, respectively; 95% CI 51-72%; $P < 0.001$]. Additionally, as compared with glyburide, metformin was associated with a 41% risk reduction in time to progression of FPG > 140mg/dl [95% CI 25-54; $P < 0.001$]. Levels of FPG and A1C decreased in all groups within the first 6 months of treatment, however the annual rate of increase in these glycemic parameters was significantly higher in the metformin and glyburide groups as

compared with *Avandia* ($P < 0.001$). A 4-year evaluation identified that significantly more participants receiving *Avandia* (40%) had an A1C < 7% as compared with metformin (36%; $P = 0.03$) and glyburide (26%; $P < 0.001$). Mean A1C < 7% was maintained for 57 months with *Avandia*, 45 months with metformin, and 33 months with glyburide.

Estimates of insulin sensitivity and β-cell function were calculated using the homeostasis model assessment (HOMA 2). Insulin sensitivity improved to a greater extent with *Avandia* than with metformin after 6 months of treatment. Thereafter, insulin sensitivity improved at similar rates in the two groups. Insulin sensitivity did not change significantly with glyburide at 4 years. There was a significant improvement in insulin sensitivity with *Avandia* as compared with both metformin (12.6%, 95% CI 8.1-17.3; $P < 0.001$) and glyburide (41.2%, 95% CI 35.2-47.4; $P < 0.001$) at 4 years. β-cell function declined in all treatment groups. The annual rate of decline after 6 months of treatment was significantly less with *Avandia* (-2.0%) as compared with metformin (-3.1%; $P = 0.02$) and glyburide (-6.1%; $P < 0.001$). Mean change in body weight from baseline was +4.8 kg with *Avandia*, -2.9 kg with metformin, and +1.6 kg with glyburide.

Cardiovascular events were reported in 4.3% (n = 62) receiving *Avandia*, 4.0% (n = 58) in the metformin group, and 2.8% (n = 41) in the glyburide group and serious cardiovascular events were reported in 3.4% (n = 49) receiving *Avandia*, 3.2% (n = 46) in the metformin group, and 1.8% (n = 26) in the glyburide group ($P \leq 0.05$ *Avandia* versus glyburide). Additionally, investigator-reported CHF occurred in 1.5% (n = 22), 1.3% (n = 19), and 0.6% (n = 9) of participants receiving *Avandia*, metformin, and glyburide, respectively ($P \leq 0.05$ *Avandia* vs glyburide) and serious investigator-reported CHF occurred in 0.8% (n = 12), 0.8% (n = 12), and 0.2% (n = 3) of participants receiving *Avandia*, metformin, and glyburide, respectively ($P \leq 0.05$ *Avandia* vs glyburide). The hazard ratio for CHF with *Avandia* as compared with metformin was 1.22 (95% CI, 0.66-2.26; $P = 0.52$) and compared with glyburide was 2.20 (95% CI 1.01-4.79; $P = 0.05$). Of the 51 possible CHF events identified by independent cardiology review of all serious adverse events, 21 were confirmed through review and involved 9 participants receiving *Avandia*, 8 receiving metformin, and 4 receiving glyburide (with 1 death).

A post-study ad hoc analysis was conducted to evaluate the ischemic cardiovascular safety events in ADOPT. [98] Results of this analysis are presented in Table 15. The analysis suggests that the risk of myocardial infarction, cardiovascular death, stroke, major adverse cardiovascular events (MACE), and total mortality in patients exposed to *Avandia* was similar to those exposed to either metformin or sulfonylurea.

**Table 15. Ischemic Cardiovascular Events in ADOPT[42,98]**

| Endpoint | Treatment | # of Events | HR(95% CI)* |
|---|---|---|---|
| Myocardial ischemia (Adverse events, non-adjudicated) | SU (n = 1441) | 82 | 1.18 (0.88-1.57) |
| | Metformin (n = 1454) | 111 | 0.99 (0.76-1.30) |
| | *Avandia* (n = 1456) | 106 | |
| Myocardial infarction or sudden death † ‡ (Serious adverse events, adjudicated) | SU (n = 1441) | 15 | 1.20 (0.62-2.35) |
| | Metformin (n = 1454) | 17 | 1.21 (0.64-2.32) |
| | *Avandia* (n = 1456) | 20 | |

HR = hazard ratio; CI = confidence interval; SU = sulfonylurea; MACE = major adverse cardiovascular event [MACE components include serious adverse events for: CV death, myocardial infarction (definite or unconfirmed) or sudden death, and stroke]

* Statistically, a hazard ratio of 1 means no difference in risk between the two agents being compared. If the confidence interval for a hazard ratio includes 1.0, there is no statistically significant difference between the rates compared. If the confidence interval for a hazard ratio does not include 1.0, that result is deemed statistically significant. † Myocardial infarction includes events adjudicated as definite or unconfirmed; ‡ Post-study ad hoc analysis

| Endpoint | Treatment | # of Events | HR(95% CI)* |
|---|---|---|---|
| Stroke‡ (Serious adverse events, non-adjudicated) | SU (n = 1441) | 12 | 0.94 (0.43-2.07) |
| | Metformin (n = 1454) | 17 | 0.77 (0.38-1.59) |
| | *Avandia* (n = 1456) | 13 | |
| CV death‡ (Serious adverse events, adjudicated) | SU (n = 1441) | 12 | 0.46 (0.17-1.23) |
| | Metformin (n = 1454) | 8 | 0.79 (0.27-2.27) |
| | *Avandia* (n =1456) | 6 | |
| MACE‡ (Serious adverse events, adjudicated MI, sudden death, and CV death, non-adjudicated stroke) | SU (n = 1441) | 28 | 1.11 (0.67-1.82) |
| | Metformin (n = 1454) | 36 | 1.00 (0.63-1.59) |
| | *Avandia* (n = 1456) | 35 | |
| Total Mortality‡ | SU (n = 1441) | 21 | 0.51 (0.25, 1.04) |
| | Metformin (n = 1454) | 15 | 0.82 (0.39, 1.76) |
| | *Avandia* (n = 1456) | 12 | |

HR = hazard ratio; CI = confidence interval; SU = sulfonylurea; MACE = major adverse cardiovascular event [MACE components include serious adverse events for: CV death, myocardial infarction (definite or unconfirmed) or sudden death, and stroke]

* Statistically, a hazard ratio of 1 means no difference in risk between the two agents being compared. If the confidence interval for a hazard ratio includes 1.0, there is no statistically significant difference between the rates compared. If the confidence interval for a hazard ratio does not include 1.0, that result is deemed statistically significant. † Myocardial infarction includes events adjudicated as definite or unconfirmed; ‡ Post-study ad hoc analysis

Edema was reported in 14.1% of participants receiving *Avandia*, 7.2% of participants receiving metformin, and 8.5% of participants receiving glyburide ($P \leq 0.01$ *Avandia* vs glyburide and vs metformin). Gastrointestinal events were less frequently reported with *Avandia* (23%) as compared to metformin (38.3%; $P \leq 0.01$). Hypoglycemia was less frequently reported with *Avandia* (9.8%) than metformin (11.6%) and glyburide (38.7%; $P \leq 0.01$). Mean alanine aminotransferase (ALT) levels decreased significantly in participants receiving *Avandia* as compared with both metformin and glyburide ($P \leq 0.01$). Low-density-lipoprotein (LDL) levels were significantly higher with *Avandia* (104 mg/dl) as compared to both metformin (96.5 mg/dl) and glyburide (99.3 mg/dl; $P \leq 0.01$).

At the time the original article was being published, further examination of the data on adverse events identified an unexpected event not part of the prespecified analysis plan. A note added in proof indicated that there was a higher incidence of fractures in patients receiving *Avandia*. There was a significantly higher incidence of fractures observed in women receiving *Avandia* as compared with either metformin or glyburide (9.3%, 5.1%, and 3.5%, respectively; $P < 0.01$). The number of men with fractures did not differ according to treatment group (4.0% with *Avandia*, 3.4% with metformin, and 3.4% with glyburide). The frequency of upper limb fractures was significantly higher in women receiving *Avandia* (3.4%) as compared with glyburide (1.5%; $P < 0.05$) while the frequency of lower limb fractures was significantly higher with *Avandia* (5.6%) as compared to both metformin (3.1%; $P < 0.05$) and glyburide (1.3%; $P < 0.01$). Upper limb fractures were reported to involve primarily the humerus and the hand while lower limb fractures involved primarily the foot. The number of women with hip fractures did not differ with *Avandia* and metformin (2 patients receiving *Avandia*, 2 receiving metformin, and none receiving glyburide). Fracture observations are under further evaluation.

**7.2 The Risk of Myocardial Ischemic Events with *Avandia* Compared to *Actos***

**Limitations of Observational Studies**

Although randomized, controlled trials are generally considered to be the best method of assessing risk, observational studies are often used to address research questions.[99] Observational studies are an important source of data to address safety related questions as they evaluate large populations of diverse individuals in a real world setting. However, observational studies can be vulnerable to methodological problems.[99,100] When evaluating observational studies, it is important to assess all possible reasons for an association including bias, confounding, chance, as well as cause.[99]

Randomized, controlled clinical trials specifically designed to evaluate the differences in the risk of myocardial ischemic events between *Avandia* and pioglitazone have not been conducted.

**Background**

Statistically, a hazard ratio (HR) of 1 means no difference in risk between the two agents being compared. If the confidence interval for a HR includes 1.0, there is no statistically significant difference between the rates compared. If the confidence interval for a HR does not include 1.0, that result is deemed statistically significant.

**Pharmetrics Study**[101,102]

An observational study was commissioned by GSK, which analyzed 402,845 patients with type 2 diabetes, using the PharMetrics Patient-Centric database, including a head-to head comparison of *Avandia* (n = 57,381) to pioglitazone (n = 51, 641). The database consists of automated claims patient data that have been aggregated from over 80 managed care databases in the United States. Between July 2000 and March 2007, new users of specific anti-diabetic regimens were identified and classified into monotherapy with *Avandia*, pioglitazone, metformin, or sulfonylurea, dual therapy with any 2 of these agents, or the use of any of these agents or other oral anti-diabetic drugs in combination with insulin. The primary outcome of the study was the first occurrence of myocardial infarction (MI) or coronary revascularization (CR). Hospital discharge diagnoses from insurance claims were used to identify new cases of MI or CR during follow-up. The average follow-up ranged from 12 to 18 months across the different cohorts. Relative risks for pair wise head-to-head comparisons within monotherapy, dual therapy, and combination with insulin cohorts were calculated using a stratified Cox-proportional hazards model, with 10 strata created from the central 90 percent of the propensity scores appropriate to each pair.

In the monotherapy cohorts, the number of patients receiving *Avandia*, pioglitazone, metformin, and sulfonylureas was 12,440, 16,302, 131,075, and 48,376, respectively. For the composite outcome of MI and/or CR, the hazard ratio (HR) for *Avandia* versus pioglitazone was 0.97 [95% confidence interval (CI): 0.78-1.20], indicating no statistically significant difference between these thiazolidinediones. Additionally, for MI alone, the HR for *Avandia* versus pioglitazone was 0.78 (95% CI: 0.52-1.18).

In the dual therapy cohorts, 36,906 patients were receiving *Avandia* in combination with metformin or sulfonylurea and 27,415 patients were receiving pioglitazone in combination with metformin or sulfonylurea. Outcome rates for the composite of MI and/or CR in patients receiving *Avandia* versus those receiving pioglitazone were similar in combination with both metformin (HR 0.97, 95% CI: 0.81-1.17) and sulfonylureas (HR 1.12, 95% CI: 0.89-1.41). Additionally, for MI alone, the outcome rates in patients receiving *Avandia* versus those receiving pioglitazone were similar in combination with both metformin (HR 1.01, 95% CI: 0.71-1.44) and sulfonylureas (HR 1.22, 95% CI: 0.83-1.78).

In the combination-with-insulin cohorts, 8,035 and 7,924 patients were receiving *Avandia* and pioglitazone, respectively. In these two groups, the risk of the composite outcome of MI and/or CR and MI alone were similar (HR 1.07 95% CI: 0.89-1.29 and HR 1.02 95% CI: 0.75-1.39, respectively).

The overall hazard ratios for the composite outcome of MI and/or CR and its individual components of MI or CR comparing all *Avandia* regimens to all pioglitazone regimens are provided in Table 16. The risk of MI, CR, and the composite outcome of MI and CR was similar between *Avandia* and pioglitazone.

**Table 16. Hazard Ratio of Composite and Individual Outcomes: *Avandia* regimens vs. Pioglitazone regimens[102]**

| | HR | 95% CI |
|---|---|---|
| MI | 1.07 | 0.89-1.27 |
| CR | 1.03 | 0.93-1.14 |
| Composite outcome: MI and CR | 1.04 | 0.94-1.14 |
| MI = myocardial infarction; CR = coronary revascularization; HR = hazard ratio; CI = confidence interval | | |

There are several limitations with regard to this analysis. In considering crude incidence rates, it is important to note that sulfonylurea initiators were generally older compared to metformin initiators, which included a relative preponderance of subjects under the age of 35. These younger patients also had fewer comorbid conditions and baseline cardiovascular risk factors. Initiators of *Avandia* and pioglitazone were more similar to one another in patient characteristics than patients on other regimens. Pioglitazone initiators had a higher prevalence of baseline hyperlipidemia than did *Avandia* initiators (48.3% for pioglitazone monotherapy compared to 42.5% for *Avandia* monotherapy). However, this difference was adjusted by including hyperlipidemia in the propensity score.

**Ingenix Study**[103]

A retrospective cohort study was conducted by Takeda Pharmaceutical Company Limited using the Ingenix database to analyze patients who initiated *Avandia* or pioglitazone between 2003-2006. The objective of this study was to compare the risk of hospitalization for acute MI in type 2 diabetes patients treated with pioglitazone relative to *Avandia*. The primary and secondary outcomes of hospitalization for acute MI, and composite of acute MI or CR were evaluated using hospital discharge diagnosis ICD-9 coding. The HR of incident hospitalization for acute MI and for the composite endpoint of acute MI or CR, in patients using pioglitazone compared to *Avandia* was estimated from multivariate Cox's proportional hazards survival analysis. Several baseline variables were considered potential risk factors for MI and were introduced into the statistical model as covariates including: age, gender, duration of diabetes drug treatment, year of index drug initiation, medical conditions and procedures such as hypertension, prior MI, prior CR, angina, unstable angina, coronary heart disease, congestive heart failure, hyperlipidemia, smoking, obesity, arrhythmias, and stroke, and dispensed drugs including metformin, sulfonylurea, meglitinides, insulin, other anti-diabetic agents, nitrates, beta-blockers, calcium-channel blockers, diuretics, angiotensin-converting enzyme (ACE)-inhibitors, angiotensin-receptor blockers, statins, fibrates, aspirin, non-steriodal antiinflammatory drugs, antiplatelet agents, and anticoagulants.

In total, 29,911 patients were included in the study with 14,807 in the pioglitazone group and 15,104 in the *Avandia* group. The groups were generally well balanced at baseline; however, the use of statins and fibrates was higher in patients receiving pioglitazone as compared with *Avandia* (statins: 39.9% vs. 34.7% and fibrates: 10.1% vs. 8.0%). Additionally, more patients in the *Avandia* group were receiving metformin (55.2% vs. 41.6%) as compared to pioglitazone. In the pioglitazone and *Avandia* groups, the average follow-up time was 1.2 years and 1.3 years, respectively.

In the group receiving pioglitazone, 161 (1.1%) patients were hospitalized for acute MI, which constitutes an unadjusted incidence rate of 93.3 (95% CI: 80.0-108.8) per 10,000 patient-years. In the *Avandia* group, 214 (1.4%) patients were hospitalized for acute MI, constituting an unadjusted incidence rate of 111.3 (95% CI: 97.0-127.1) per 10,000 patient years. The unadjusted HR for hospitalization for acute MI for pioglitazone relative to *Avandia* was 0.82 (95% CI: 0.67-1.01), indicating no statistically significant difference between the groups, and 0.78 (95% CI: 0.63-0.96) after adjusting for the baseline covariates described above. There were 386 (2.6%) patients in the pioglitazone group and 468 (3.1%) in the *Avandia* group with a first event in the composite endpoint of acute MI or CR. The adjusted HR was 0.85 (95% CI: 0.75-0.98).

To assess the differences in baseline use of metformin and lipid lowering agents, sensitivity analyses were conducted. The HR for patients in the pioglitazone group relative to the *Avandia* group who were receiving metformin at baseline was 0.85 (95% CI: 0.62-1.19), while the HR was 0.74 (95% CI: 0.56-0.97) for those who were not receiving metformin. Among patients who were receiving statins or fibrates at baseline, the HR for acute MI was 0.59 (95% CI: 0.43-0.81). However, among patients who were not

taking these agents at baseline, there was no difference in acute MI between the pioglitazone and *Avandia* groups [HR 0.96 (95% CI: 0.73-1.26)].

Several aspects of this study create potential bias. The use of lipid lowering agents is known to help reduce the risk of MI, and in this study, the use of statins and fibrates was higher in the pioglitazone group compared to the *Avandia* group. In addition, the study does not distinguish between results for patients taking pioglitazone and *Avandia* as monotherapy, dual therapy, and combinations with insulin. Therefore, the mix of therapies was unknown between the groups. Patients on combination therapy may have more progressive disease and may be at a greater risk of events. A difference in the distribution of monotherapy, dual therapy, and combination therapy with insulin between the groups may have contributed to the difference in outcomes between pioglitazone and *Avandia*.

**Wellpoint Cohort Study**

A retrospective-longitudinal cohort study was conducted by HealthCore, the health outcomes research subsidiary of WellPoint.[104] WellPoint is a health benefits company providing health coverage to over 34 million Americans. This study was entirely funded by WellPoint and conducted to determine if there is evidence in a real world setting of elevated risk of myocardial infarction (MI) in patients receiving *Avandia* or pioglitazone. The primary objective was to determine the risk of acute MI in patients taking *Avandia* or pioglitazone compared to patients taking other oral antidiabetic agents (OADs). Details of this study are limited to what was presented at the Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee on July 30, 2007.

The study used integrated health claims data including pharmacy, medical, and member eligibility for five of WellPoint's plans from January 1, 2001 through December 31, 2006. The *Avandia* cohort included patients taking *Avandia* as monotherapy or in combination with other OADs. Similarly, the pioglitazone cohort included patients taking pioglitazone as monotherapy or in combination with other OADs. Subjects taking insulin or both TZD's during the evaluation period were excluded. Acute MI was determined by review of all medical claims for care in the hospital or emergency room using ICD-9 codes (410.XX). As part of the sensitivity analysis, the definition of acute MI was expanded to include unstable angina (ICD-9 code 411.1X). The severity of illness, complications and intensity of diabetes were determined by evaluation of covariates including markers of cardiovascular (CV) risk in the year prior to initiating therapy.

Multivariate Cox-proportional hazards modeling was used to evaluate the independent effects of exposure to *Avandia*, pioglitazone, and other OADs on the risk of acute MI. Baseline CV risk factors were adjusted for using the CV risk score. In addition, extensive sensitivity analyses were conducted to assess the impact of definition of outcome and exposures.

The study sample included 22,050 users of *Avandia*, 23,768 users of pioglitazone, and 120,771 users of other OADs. Patients taking *Avandia* and pioglitazone were significantly older and had a higher burden of comorbidities than patients taking all other OADs. Patients taking *Avandia* and pioglitazone had a significantly higher pre-index CV disease and CV medication utilization. A statistically significant greater use of angiotensin-receptor blockers, beta-blockers, calcium-channel blockers and lipid-altering medications was observed in the pioglitazone cohort compared to the *Avandia* cohort ($P < 0.05$ for each medication). Both *Avandia* and pioglitazone patients had almost twice the diabetic hospitalizations and a greater burden of complications including retinopathy and nephropathy compared to patients treated with OADs prior to treatment.

The number of incident acute MIs excluding angina was 212 for *Avandia* , 232 for pioglitazone, and 866 for other OADs. The incidence rates of acute MI were 0.73, 0.74, and 0.72 per 100 patient years for *Avandia*, pioglitazone, and other OADs, respectively. When angina was included, the incidence rates were 1.43, 1.33, and 1.34 per 100 patient years, respectively as above. The adjusted hazard ratio (HR) for acute MI for patients treated with *Avandia* compared to other OADs was 1.029 ($P = 0.710$) and 1.044 ($P = 0.553$) in patients treated with pioglitazone (Table 17).

**Table 17. Adjusted Hazard Ratios of Acute MI including and Excluding Unstable Angina for Avandia, Pioglitazone and Other OADs[104]**

| | Acute MI = 410.XX (ICD-9 code) | | | Acute MI = 410.XX or 411.1X | | |
|---|---|---|---|---|---|---|
| | **HR** | **95% CI** | **P- value** | **HR** | **95% CI** | ***P*- value** |
| *Avandia* | 1.029 | 0.886-1.194 | 0.710 | 1.086 | 0.979-1.205 | 0.117 |
| Pioglitazone | 1.044 | 0.905-1.205 | 0.553 | 0.987 | 0.890-1.095 | 0.808 |
| OADs | reference | reference | reference | reference | reference | reference |
| CI = Confidence interval; HR = Hazard ratio; MI = Myocardial infarction; OADs = Oral antidiabetic agents | | | | | | |

Compared to oral antidiabetic agents, the adjusted HR for acute MI excluding angina for monotherapy cohorts (almost 6,000 for *Avandia* and 9,000 for pioglitazone) was 0.977 in patients taking *Avandia* and 0.861 in patients taking pioglitazone, neither one was statistically significant (Table 18).

**Table 18. Adjusted Hazards Ratios of Acute MI including and Excluding Unstable Angina in Monotherapy Cohorts for *Avandia*, Pioglitazone, and Other Oral Antidiabetic Agents[104]**

| | Acute MI = 410.XX (ICD-9 code) | | | Acute MI = 410.XX or 411.1X | | |
|---|---|---|---|---|---|---|
| | **HR** | **95% CI** | ***P*- value** | **HR** | **95% CI** | ***P*-value** |
| *Avandia* | 0.977 | 0.734 – 1.301 | 0.874 | 1.159 | 0.963 – 1.395 | 0.118 |
| Pioglitazone | 0.861 | 0.610 – 1.216 | 0.396 | 0.912 | 0.720 - 1.155 | 0.445 |
| Other OADs | reference | reference | reference | reference | reference | reference |
| CI = Confidence interval; HR = Hazard ratio; MI = Myocardial infarction; OADs = Oral antidiabetic agents | | | | | | |

When the analysis was limited to that of drug treatment period, the HR for acute MI was 0.945 for *Avandia* and 0.90 for pioglitazone with no statistical significance (Table 19).

**Table 19. Adjusted HR of Acute MI Including and Excluding Unstable Angina for *Avandia*, Pioglitazone, and Other Oral Antidiabetic Agents Limited to Treatment Period[104]**

| | Acute MI = 410.XX (ICD-9 code) | | | Acute MI = 410.XX or 411.1X | | |
|---|---|---|---|---|---|---|
| | **HR** | **95% CI** | ***P*- value** | **HR** | **95% CI** | ***P*-value** |
| *Avandia* | 0.945 | 0.656 – 1.362 | 0.762 | 0.959 | 0.764 – 1.203 | 0.718 |
| Pioglitazone | 0.900 | 0.633 – 1.278 | 0.555 | 0.811 | 0.646 - 1.020 | 0.073 |
| Other OADs | reference | reference | reference | reference | reference | reference |
| CI = Confidence interval; HR = Hazard ratio; MI = Myocardial infarction; OADs = Oral antidiabetic agents | | | | | | |

The WellPoint investigators reported that they did not identify a statistically significant increase in the risk for acute cardiac events, including MI and unstable angina, in patients who received *Avandia* or pioglitazone when compared to patients taking other oral anti-diabetic agents.[104] In addition, a sub-cohort of patients treated with *Avandia* or pioglitazone as monotherapy were also found to not have an elevated risk of acute cardiac events.

**Tricare Study**[105,106]

The Department of Defense conducted a cross-sectional analysis of data from fiscal years 2003-2006 to determine if there was an increased incidence of acute MI and CHF among Military Health System (MHS) beneficiaries who filled a prescription for *Avandia* compared to those who filled a prescription for other antidiabetic medications. The MHS provides health coverage to approximately 9.1 million beneficiaries. The data for the analysis was collected from enrollees of TRICARE Prime, which is a managed care option similar to a civilian health maintenance organization. The study was limited to individuals younger than 65 years of age since older individuals are not eligible for TRICARE Prime. This information was presented at the Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee on July 30, 2007 and recently published in the *American Journal of Therapeutics*.

The analysis used three different data sources: Defense Eligibility Enrollment System (DEERS), inpatient/outpatient encounter claims, and Pharmacy Data Transaction Service (PDTS). DEERS provided data necessary for the establishment of demographic characteristics of the population. The inpatient/outpatient encounter claims included the date and source of service received, diagnoses of diseases according to ICD-9 and procedure codes (DRG). PDTS allowed tracking of the real time prescription fill records regardless of sources of fill. The three data sources were linked by identifiers.

Type 2 diabetes was defined using the ICD-9 code. Individual drugs were grouped into therapeutic classes of antidiabetic drugs. The drug categories defined were not mutually exclusive, and therefore, statistical comparisons of the drugs analyzed were not preformed. Incident cases of acute MI and CHF were identified using the earliest date of diagnosis.

In total, 231,962 diabetic patients were included in the study of which 46% were male and 54% were female. Approximately 70% of the individuals in the study were between 45 and 64 years of age.Table 20 provides the annual incidence rates of acute MI averaged over the 4 year period of the study.

**Table 20. Annual Incidence Rates of Acute Myocardial Infarction Averaged Over the 4 Year Period in TRICARE Prime (2003-2006)** [105,106]

| | | Acute MI | |
|---|---|---|---|
| | N Dispensed Drug | N | Average Annual Incidence per 10,000 |
| Any TZD | 20,002 | 299 | 37.37 |
| *Avandia* | 13,400 | 202 | 37.69 |
| Pioglitazone | 7,831 | 111 | 35.44 |
| Biguanides | 58,091 | 769 | 33.09 |
| Sulfonylureas | 23,520 | 457 | 48.58 |
| Insulin | 11,854 | 245 | 51.67 |
| Nitrates | 6561 | 831 | 316.64 |
| *Avandia* + nitrates | 1320 | 177 | 335.23 |
| Pioglitazone + nitrates | 891 | 131 | 367.56 |

The authors concluded that there was no increased annual incidence of acute MI among TRICARE Prime beneficiaries with a diagnosis of type 2 diabetes who have filled a prescription for *Avandia* compared with those who filled prescriptions for other antidiabetic medications.

There were several limitations to this study. The study did not adjust for potential confounding factors such as socioeconomic status, comorbid conditions, current health status, medical history, drug dose, time on drug, concurrent medications, or individual characteristics such as body mass index, diet, smoking, and exercise. Therefore, it was not possible to determine whether the observed differences in average annual incidence rates of the outcomes were due to the inherent differences in antidiabetic drugs or other confounding factors such as disease progression, other risk factors for cardiovascular events such as age, and the differences in the number, type, and severity of comorbid conditions. The study also did not include individuals who were 65 years of age and older. The outcome of acute MI was attributed to the antidiabetic class if the prescription was filled at any time prior to the event, assuming a cause-effect relationship. An additional limitation was that the drug categories were not mutually exclusive and therefore statistical comparisons for significance were not possible.

**Integrated Healthcare Information Services (IHCIS) Study**[107,108]

An observational study was conducted using the Integrated Healthcare Information Services (IHCIS) database, a U.S. managed care claims database which contains data on 891,901 patients with type 2 diabetes. The study was a case-control analysis nested within the cohort of eligible type 2 diabetic patients captured in IHCIS from 1999-2006. The study was designed to determine the odds of MI in patients with type 2 diabetes exposed to thiazolidinediones (TZDs) (*Avandia* and pioglitazone, separately) compared to those exposed to other anti-diabetic agents. Incident cases of hospitalization for MI were identified among type 2 diabetic patients. Three controls were matched to each case based on age (+/- 5 years), gender, calendar year of diabetes diagnosis, and year of MI diagnosis (index year). The odds of MI were modeled using conditional logistic regression, adjusting for age, gender, ACE-inhibitor use, beta-blocker use, diuretic use, nitrate use, and hyperlipidemia and hypertension diagnosis.

The incidence rate of MI in the diabetic cohort was 5.25 per 1,000 person-years (95% CI: 5.15-5.36). The average follow-up was 2.1 years, during which 9,870 MI cases (1.1%) were identified and matched to 29,610 controls. In the 3 months prior to the index date (recent exposure), 1,149 (11.6%) cases and 2,690 (9.1%) controls were exposed to *Avandia*, 910 (9.2%) cases and 2,433 (8.2%) controls were exposed to pioglitazone, and 5,644 (57.2%) cases and 13,702 (46.3%) controls were treated with other anti-diabetic therapies excluding TZDs. The risk of MI in patients exposed to either *Avandia* or pioglitazone compared

with those patients exposed to other anti-diabetic therapies was 1.03 (95% CI: 0.99-1.12) and 0.92 (95% CI: 0.83-1.01), respectively. The risk of MI in subjects exposed to *Avandia* or pioglitazone for ≤ 12 months is not different from those exposed to other antidiabetic agents but exposure for >12 months is associated with a 15% and 13% increased risk of MI, respectively.

A limitation to this analysis is the utilization of a nested-case control study design. Results of cohort studies utilizing propensity scores represent a higher level of study design and evidence.

**Institute for Clinical Evaluative Sciences (ICES) Study**[109]

A population-based, retrospective nested case-control cohort study was conducted using health care databases from Ontario, Canada to evaluate the risks of congestive heart failure (CHF), acute MI, and all-cause mortality associated with the use of TZDs compared to other oral hypoglycemic drug combination therapies. Of note, reimbursement for TZDs during the time of the study was restricted to patients experiencing uncontrolled hyperglycemia or to those who had a contraindication or intolerance to metformin and/or sulfonylureas. The study population included diabetic patients from Ontario who were 66 years of age or older treated with at least 1 oral hypoglycemic drug between April 1, 2002 and March 31, 2005. Patients who were treated with insulin in the year prior to cohort entry were excluded, while patients who began treatment with insulin during follow-up were retained in the study. Patients were followed up until they experienced an event, death, a last health services contact in Ontario (for those who lost health contact for at least 6 months), or March 31, 2006, whichever occurred first. The primary outcome of the study was a first hospital visit for CHF defined as an emergency room visit for CHF or a hospital admission with CHF as the discharge diagnosis. The secondary study outcomes were a hospital visit for acute MI, defined as either an emergency room visit for MI or a hospital admission with MI as the discharge diagnosis, and all-cause mortality.

The study population consisted of 159,026 diabetic patients who were treated with oral hypoglycemic agents. The mean age of the individuals included in the study was 74.7 years, and the median follow-up for the study was 3.8 years. A greater proportion of patients taking TZD monotherapy had a history of renal and cardiovascular disease compared with those receiving TZD combination therapy and other oral antidiabetic agent combination therapy. Patients receiving *Avandia* monotherapy had greater comorbidity compared with those prescribed pioglitazone monotherapy, although the proportion with a history of cardiovascular disease was similar. All other baseline characteristics were similar between the groups. Cases and controls were well matched for age, sex, cardiovascular history, and duration of diabetes; however, the occurrence of noncardiac comorbidity was somewhat higher among cases than controls.

Overall, 7.9% of patients (n = 12,491) had a hospital visit for CHF, 7.9% for acute MI (n = 12,578), and 19% died (n = 30,265). Compared with patients receiving other oral hypoglycemic agent combination therapy, current users of TZD monotherapy and combination therapy were at an increased risk of CHF and death. An increased risk of acute MI was seen with current use of TZD monotherapy, but not TZD combination therapy, compared to use of other oral hypoglycemic agent combinations. The association between CHF, acute MI, and mortality and TZD therapy appeared to be limited to treatment with *Avandia*; however, there was limited power to explore the association between outcomes and the use of pioglitazone due to the smaller number of patients taking pioglitazone. Table 21 summarizes the results for acute MI and mortality.

**Table 21. Rate Ratios of Acute Myocardial Infarction and All-Cause Mortality With the Use of Thiazolidinediones Compared to Other Oral Hypoglycemic Agent Combination Therapies[109]**

| | Number of Cases | Number of Controls | Unadjusted Rate Ratio (95% Confidence Interval)* | Adjusted Rate Ratio (95% Confidence Interval)*† | *P* Value for Adjusted Rate Ratio |
|---|---|---|---|---|---|
| **Acute Myocardial Infarction** | | | | | |
| Current Other OHA Combination Therapy‡ | 3695 | 18351 | | | |
| Current TZD monotherapy§ | 65 | 228 | 1.42 (1.08-1.88) | 1.40 (1.05-1.86) | 0.02 |
| *Avandia* | 53 | 147 | 1.80 (1.31-2.46) | 1.76 (1.27-2.44) | <0.001 |
| Pioglitazone | 12 | 81 | 0.74 (0.41-1.37) | 0.73 (0.40-1.36) | 0.33 |
| Current TZD Combination Therapy | 404 | 2109 | 0.96 (0.86-1.07) | 0.96 (0.85-1.08) | 0.49 |
| *Avandia* | 282 | 1404 | 1.00 (0.88-1.15) | 1.00 (0.87-1.16) | 0.96 |
| Pioglitazone | 122 | 705 | 0.87 (0.72-1.06) | 0.87 (0.71-1.06) | 0.17 |
| Past Treatment with TZDs‖ | 140 | 630 | 1.11 (0.92-1.34) | 1.05 (0.87-1.28) | 0.62 |
| *Avandia* | 95 | 424 | 1.12 (0.90-1.41) | 1.06 (0.84-1.34) | 0.65 |
| Pioglitazone | 45 | 206 | 1.10 (0.79-1.52) | 1.04 (0.75-1.45) | 0.81 |
| **All-Cause Mortality** | | | | | |
| Current Other OHA Combination Therapy‡ | 5529 | 18835 | | | |

OHA - Oral hypoglycemic agent; TZD - Thiazolidinedione

*All models were also adjusted for current insulin combination therapy (cases = 370; controls = 1084), insulin monotherapy (cases = 361; controls = 1010), other OHA monotherapy (cases = 7667; controls = 40108), and no current therapy (cases = 1803; controls = 8400).

†Adjusted for income quintile; residence in long-term care facility; Charlson comorbidity score category; history of use of angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, β-blockers, calcium channel blockers, diuretics, spironolactone, statins, and digoxin; prior metformin use; prior sulfonylurea use; prior use of other OHAs; prior use of TZDs; congestive heart failure in past year and in past 1-5 years; angina in past year and in past 1-5 years; coronary artery bypass graft surgery in past year and in past 1-5 years; coronary catheterization in past year and in past 1-5 years; percutaneous transluminal coronary angioplasty in past year and in past 1-5 years; history of renal disease; and number of drugs prescribed in prior 6 months.

‡Other than TZDs; more than 97% were receiving metformin + sulfonylurea.

§Current users are those who were dispensed the drug with the days supplied overlapping the index date by 14 days or more.

‖Past users are those who were dispensed the drug with the days supplied ending between 15 and 365 days before the index date.

| | Number of Cases | Number of Controls | Unadjusted Rate Ratio (95% Confidence Interval)* | Adjusted Rate Ratio (95% Confidence Interval)*† | *P* Value for Adjusted Rate Ratio |
|---|---|---|---|---|---|
| Current TZD monotherapy§ | 102 | 392 | 0.85 (0.68-1.06) | 1.29 (1.02-1.62) | 0.03 |
| *Avandia* | 76 | 255 | 0.99 (0.76-1.29) | 1.47 (1.12-1.93) | 0.005 |
| Pioglitazone | 26 | 137 | 0.60 (0.39-0.91) | 0.94 (0.61-1.45) | 0.78 |
| Current TZD Combination Therapy | 497 | 1440 | 1.17 (1.05-1.30) | 1.24 (1.11-1.39) | <0.001 |
| *Avandia* | 358 | 1027 | 1.18 (1.04-1.34) | 1.26 (1.10-1.44) | <0.001 |
| Pioglitazone | 139 | 413 | 1.15 (0.94-1.40) | 1.20 (0.98-1.47) | 0.08 |
| Past Treatment with TZDs‖ | 458 | 807 | 1.93 (1.71-2.18) | 2.08 (1.82-2.37) | <0.001 |
| *Avandia* | 314 | 576 | 1.85 (1.61-2.14) | 1.98 (1.70-2.31) | <0.001 |
| Pioglitazone | 144 | 231 | 2.14 (1.73-2.65) | 2.32 (1.85-2.90) | <0.001 |

OHA - Oral hypoglycemic agent; TZD - Thiazolidinedione

*All models were also adjusted for current insulin combination therapy (cases = 370; controls = 1084), insulin monotherapy (cases = 361; controls = 1010), other OHA monotherapy (cases = 7667; controls = 40108), and no current therapy (cases = 1803; controls = 8400).

†Adjusted for income quintile; residence in long-term care facility; Charlson comorbidity score category; history of use of angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, β-blockers, calcium channel blockers, diuretics, spironolactone, statins, and digoxin; prior metformin use; prior sulfonylurea use; prior use of other OHAs; prior use of TZDs; congestive heart failure in past year and in past 1-5 years; angina in past year and in past 1-5 years; coronary artery bypass graft surgery in past year and in past 1-5 years; coronary catheterization in past year and in past 1-5 years; percutaneous transluminal coronary angioplasty in past year and in past 1-5 years; history of renal disease; and number of drugs prescribed in prior 6 months.

‡Other than TZDs; more than 97% were receiving metformin + sulfonylurea.

§Current users are those who were dispensed the drug with the days supplied overlapping the index date by 14 days or more.

‖Past users are those who were dispensed the drug with the days supplied ending between 15 and 365 days before the index date.

This study contains significant limitations which could have biased the results. The database used in this study is composed of a select group of patients. During the study, TZDs were restricted to those patients who failed treatment on metformin and sulfonylurea or for whom sulfonylurea or metformin were contraindicated. Therefore, TZD patients had a higher baseline risk for cardiovascular disease, and the use of TZDs in this database does not reflect the real world use. Patients who were prescribed *Avandia* monotherapy suffered from more chronic diseases compared with those prescribed pioglitazone monotherapy, and therefore, were sicker patients. This difference is not corrected for in the analysis of the data and in the study conclusions. In addition, the TZD monotherapy group had a 3 to 4-fold higher rate of renal impairment, which is indicative of patients with more progressive type 2 diabetes. Furthermore, the authors state that the study may have been underpowered to detect adverse effects associated with pioglitazone due to the relatively small number of patients prescribed this agent. It is stated that larger studies are needed to better determine the relative effect of each agent on cardiovascular outcomes.

**An Innapropriate Comparison Between Meta-analyses**

Two meta-analyses were published side by side in the September 12, 2007 edition of the Journal of the American Medical Association (JAMA). One meta-analysis conducted by Singh, et al, assessed the long-term risk of cardiovascular events with *Avandia*, utilizing the endpoints of myocardial infarction, heart failure, and cardiovascular mortality.(110) In this analysis the relative risk (RR) for MI for *Avandia* (n = 94/6421) compared to control (n = 83/7870) was 1.42 (95% CI: 1.06-1.91; *P* = 0.02). The RR of heart failure with *Avandia* (n = 102/6421) compared to control (n = 62/7870) was 2.09 (95% CI: 1.52-2.88; *P*<0.001). There was no significant risk of cardiovascular mortality with *Avandia* (n = 59/6421) compared to control (n = 72/7870) (RR 0.90; 95% CI: 0.63-1.26; *P* = 0.53). The other meta-analysis conducted by Lincoff et al, evaluated a composite endpoint of death, myocardial infarction, or stroke in patients treated with pioglitazone.(111) The composite endpoint occurred in 4.4% (n = 375/8554) of patients receiving pioglitazone and 5.7% (n = 450/7836) of patients receiving control therapy (HR 0.82; 95% CI: 0.72-0.94; *P* = 0.005).

These articles appear to be written and published in a manner meant to draw comparisons between *Avandia* and pioglitazone that cannot be made for many reasons, including:

• Each meta-analysis used a set of clinical trials that studied different populations, some studying drug-naïve patients, while others studied patients on insulin or with documented histories of cardiovascular events

• The endpoints used in each of the trials, and each of the meta-analyses were different

• The duration, event rate, analysis method, and event definitions varied across trials

The pioglitzone meta-analysis is based on a small number of studies (19), and is heavily influenced by data from the PROactive study (5,238 patients) which contributed 32% of the entire population of the meta-analysis and 55% of the patient-years.(111) PROactive compared diabetic patients who were randomly assigned to pioglitazone or placebo in addition to their existing antidiabetic medications.(112)

No statistical difference between *Avandia* and comparators was observed when the endpoint of CV death, myocardial infarction and stroke are applied to the data on *Avandia* , across long-term clinical trials (HR 1.03).(113) In RECORD, a study specifically designed to look at cardiovascular events, no appreciable difference was seen between *Avandia* and comparators (HR 0.96).(56) These results are similar to the results from the meta-analysis conducted by Lincoff et al , which observed HR 0.82 in patients treated with pioglitazone.(111)

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with *Avandia* or any other oral antidiabetic drug.(42)

## 8. OUTCOME AND ECONOMIC EVALUATION

### Background

An estimated 20.8 million Americans are affected by Diabetes. (21) Type 2 diabetes accounts for 90 to 95% of all diagnosed diabetes cases and affects more than 18 million people in the United States. (114) The American Diabetes Association (ADA) has estimated the total cost (direct and indirect) attributable to diabetes to be $132 billion in 2002. (21) Over two-thirds of these costs were direct medical costs such as those due to hospitalization, outpatient visits, and the rest were indirect costs such as those due to lost productivity.

Health problems from diabetes are a serious issue in the U.S. (114) The State of Diabetes Complications in America report shows that 3 out of 5 people with type 2 diabetes has at least one of the serious health problems connected to the disease such as, heart disease, stroke, eye damage, kidney disease, and foot problems that can lead to amputation. Estimated annual healthcare costs for a person with diabetes and its related complications are about three times that of the average American without diagnosed diabetes.

Large-scale studies have demonstrated that tight glycemic control greatly reduces the frequency and severity of long-term diabetes-related complications. In the 10-year United Kingdom Prospective Diabetes Study (UKPDS), intensive glycemic control resulted in HbA1c levels that were significantly lower than in patients on conventional therapy.(115) According to the UKPDS 35 Study, every 1% decrease in HbA1c

resulted in a 21% decrease in risk of any diabetes-related end point. [116] The primary goal of diabetes therapy should be to prevent the occurrence of diabetic complications by enhanced glycemic control and treatment of insulin resistance.

**Treatment Adherence with *Avandia***

A retrospective cohort study was conducted using patient data from the North Carolina Medicaid program database queried from July 1, 2001 to June 30, 2002.[117] Patients were followed up for complete healthcare service utilization (hospitalizations, emergency department visits, outpatient physician visits, utilization of antidiabetic medication) and costs. Measures of adherence (medication possession ratio) and persistence (index of treatment persistence) were used to assess utilization of antidiabetic medication. Total annual healthcare costs were compared for Medicaid recipients newly started on thiazolidinediones (TZDs) vs. other oral antidiabetic agents. When healthcare costs were compared for Medicaid recipients newly started on TZDs vs. other oral antidiabetic agents, cost savings were realized for the TZD cohort as early as 2 years following therapy initiation ($9,458 vs. $10,629, $P < 0.05$). Patients starting TZDs had 16% lower total annual healthcare costs compared to patients starting other oral antidiabetics ($P < 0.01$). The persistence and adherence rates for the TZD group were statistically significantly higher than the oral antidiabetics group at nearly 9% and 13%, respectively ($P < 0.01$). The subanalysis comparing the two TZDs, *Avandia* and pioglitazone, showed no significant differences between the two TZD groups in total annual healthcare costs, treatment adherence, or persistence rates.

An extended analysis was conducted to examine the original cohort of patients for an additional 18 months (up to December 2004) of observational follow-up. [118] Average healthcare costs for patients on a TZD were less compared to the metformin and other sulfonylurea groups ($P < 0.05$). Overall, TZD's were associated with improved adherence but not persistence.

A separate analysis utilizing the same Medicaid database compared healthcare utlilization and costs associated with initiation of treatment with either *Avandia* or pioglitazone in type 2 diabetes patients.[119] *Avandia* monotherapy was associated with a 12.2% decrease in the mean number of hospitalizations, a 10.4% decrease in mean number of emergency department visits, and 7.3% decrease in total healthcare costs compared with the pioglitazone monotherapy group ($P < 0.05$ for all comparisons).

**Resource Utilization and Cost of Care with *Avandia***

The RESULT (Rosiglitazone Early vs. SULfonylurea Titration) trial demonstrated that combination therapy of *Avandia* and a sulfonylurea (SU; glipizide) has potential to reduce health service utilization and cost of care in type 2 diabetes if compared to progressive titration of an SU (glipizide). [20] In this study, patients on glipizide 10 mg twice daily were randomized to the addition of *Avandia* (4 mg once daily to 8 mg once daily as needed) before titration of glipizide, or to continued up-titration of glipizide, to a maximum of 40 mg/day. Over a 2-year study period, in addition to superior glycemic control, combination therapy with *Avandia* and SU was associated with significantly fewer emergency department (ED) visits (0.59 vs. 1.47 per 1000 patient-days, $P = 0.0006$) and hospitalizations (0.37 vs. 0.76 per 1000 patient days, $P = 0.0263$) compared to SU monotherapy. Despite higher pharmacy costs, total direct per patient per month (PPPM) healthcare costs were also significantly lower with *Avandia* and SU therapy compared to SU monotherapy ($480 vs. $645 PPPM, $P < 0.05$).

## 9. ECONOMIC MODEL

### *AVANDARYL*: ECONOMIC MODEL

**Purpose**

The purpose of the budget impact model is to compare the amount spent on oral antidiabetic agents for people with type 2 diabetes who are not controlled with sulfonylurea (SU) monotherapy, before and after the introduction of *Avandaryl*. This information will help decision makers understand the impact of a new fixed-dose combination and will allow for estimation of the economic impact of adoption of *Avandaryl* relative to Amaryl® (glimepiride, Aventis), Actos® (pioglitazone, Takeda Pharmaceuticals America, Inc.) plus glimepiride, Avandia® (rosiglitazone) and plus glimepiride under a pre-defined utilization scenario in a Medicaid population for patients who are not controlled with SU monotherapy.

**Methods**

GlaxoSmithKline developed the model using Microsoft Excel. The model estimates the number of patients in a Medicaid population who have type 2 diabetes and are not controlled with SU (glimepiride) monotherapy. This model calculates drug costs for *Avandaryl*, glimepiride, pioglitazone plus glimepiride, and rosiglitazone plus glimepiride based on wholesale acquisition cost (WAC), daily average consumption (DACON) estimates, and the distribution of the population taking each dose combination.

The following parameters are used in the model:

1. The total number of people in the Medicaid population (n = 500,000).
2. The prevalence of diagnosed type 1 and type 2 diabetes (the default is 6%).
3. The prevalence for type 2 diabetes (the default is 90%).
4. The percentage of type 2 diabetes patients who are not controlled with SU monotherapy (the default is 10%).
5. The pricing information for each drug (the default is WAC, Wolters-Kluwer, 7/21/2005).
6. The distribution of patients according to the dosage form of each drug (the default is based on DACON estimates from Verispan SPA MAT, 9/30/2005).
7. The percentage of patients taking each drug before and after changes in the market distribution (Table 22).

**Table 22. Percentage of Patients on Each Product (hypothetical distribution)**

| | Beginning Market Share | Ending Market Share |
|---|---|---|
| ***Avandaryl*** | 0% | 18% |
| **Glimepiride** | 80% | 78% |
| **Pioglitazone + Glimepiride** | 10% | 2% |
| **Rosiglitazone + Glimepiride** | 10% | 2% |

Table 23 below illustrates the average cost per person per day of *Avandaryl*, glimepiride, pioglitazone plus glimepiride, and rosiglitazone plus glimepiride. For these particular combinations, the following assumptions were made:

Wholesale Acquisition Cost of *Avandaryl*:

- 4 mg/1 mg: $3.22/tablet
- 4 mg/2 mg: $3.22/tablet
- 4 mg/4 mg: $3.22/tablet

Wholesale Acquisition Cost of glimepiride:

- 1 mg: $0.36/tablet
- 2 mg: $0.58/tablet
- 4 mg: $1.09/tablet

Wholesale Acquisition Cost of pioglitazone:

- 15 mg: $3.13/tablet
- 30 mg: $5.01/tablet
- 45 mg: $5.44/tablet

Wholesale Acquisition Cost of rosiglitazone:

- 2 mg: $1.76/tablet
- 4 mg: $2.51/tablet
- 8 mg: $4.66/tablet

DACON for pioglitazone plus glimepiride and rosiglitazone plus glimepiride: 1.0 at all dose combinations

**Table 23. Average Cost Per Day of Therapies of Interest**

| | DACON | $Cost/tablet | Average $Cost/person/day |
|---|---|---|---|
| ***Avandaryl*** | | | |
| 4 mg/1 mg | 1.7 | $3.22 | $5.47 |
| 4 mg/2 mg | 1.5 | $3.22 | $4.83 |
| 4 mg/4 mg | 1.2 | $3.22 | $3.86 |
| **Glimepiride** | | | |
| 1 mg | 1.1 | $0.36 | $0.40 |
| 2 mg | 1.1 | $0.58 | $0.64 |
| 4 mg | 1.4 | $1.09 | $1.53 |
| **Pioglitazone + Glimepiride** | | | |
| 15 mg + 4 mg | 1 | $4.22 | $4.22 |
| 15 mg + 8 mg | 1 | $5.31 | $5.31 |
| 30 mg + 4 mg | 1 | $6.10 | $6.10 |
| 30 mg + 8 mg | 1 | $7.19 | $7.19 |
| 45 mg + 8 mg | 1 | $7.62 | $7.62 |
| **Rosiglitazone + Glimepiride** | | | |
| 4 mg + 2 mg | 1 | $3.09 | $3.09 |
| 4 mg + 4 mg | 1 | $3.60 | $3.60 |
| 4 mg + 8 mg | 1 | $4.69 | $4.69 |
| 8 mg + 4 mg | 1 | $5.75 | $5.75 |
| 8 mg + 8 mg | 1 | $6.84 | $6.84 |

**Key Assumptions**

The scenario presented below includes assumptions that were developed from product information and published literature. First, it was assumed that there were 500,000 Medicaid recipients in the state. The prevalence of diabetes among them was assumed to be 6%. The vast majority (90%) were assumed to have type 2 diabetes, of whom 10% were assumed to be inadequately controlled with SU monotherapy.

**Model Results**

Table 24 summarizes the economic impact given the assumption of the model with a cohort of 2,700 patients with type 2 diabetes who are not controlled with SU monotherapy. Differences in costs were estimated for *Avandaryl*, glimepiride, pioglitazone plus glimepiride, and rosiglitazone plus glimepiride and are summarized below.

**Table 24. Patients Not Controlled with Glimepiride Monotherapy - Estimated Total Economic Impact**

| | Beginning Market Share | Cost | Ending Market Share | Cost | Cost Savings |
|---|---|---|---|---|---|
| ***Avandaryl*** | 0% | $0 | 18% | $759,348 | |
| **Glimepiride** | 80% | $921,365 | 78% | $898,331 | |
| **Pioglitazone + glimepiride** | 10% | $551,486 | 2% | $110,297 | |
| **Rosiglitazone + glimepiride** | 10% | $481,890 | 2% | $96,378 | |
| **Totals** | 100% | *$1,954,741* | 100% | *$1,864,354* | **$90,387** |
| | | | | | **4.62%** |

Based on the default scenario, the introduction of *Avandaryl* to the formulary will save over 4.6% in drug costs in the environment where patients are prescribed glimepiride, pioglitazone plus glimepiride combination therapy, or rosiglitazone plus glimepiride combination therapy. Using only WAC as a default, the use of *Avandaryl* compared to the other combination therapies may result in a significant decrease in pharmacy expenditures. This represents an overall reduction in Medicaid pharmacy costs of $90,387 or 4.62%.

This hypothetical scenario assumes that *Avandaryl* receives approximately 80% of pioglitazone plus glimepiride combination therapy and rosiglitazone plus glimepiride combination therapy market share, and glimepiride market share is reduced from 80% to 78%.

**Discussion of Model Results**

Increase in use of *Avandaryl* provides an opportunity to reduce Medicaid pharmacy costs and provide better glycemic control to patients in a convenient dose. While this model has shown reductions in overall pharmacy costs with the introduction of *Avandaryl*, it does not account for the potential improvement in compliance with a fixed-dose combination product over combination therapy as separate tablets, nor does it account for potential reduction in the rate of long-term type 2 diabetes complications associated with durable glycemic control. These are two potential benefits of *Avandaryl* and may lead to overall reduction in utilization of medical services due to potential improvements in glycemic control and side effects.

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